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AN ATTEMPT ON THE SYNTHESIS OF THE CLAVAM SKELETON FROM GLYCALS AND ISOCYANATES

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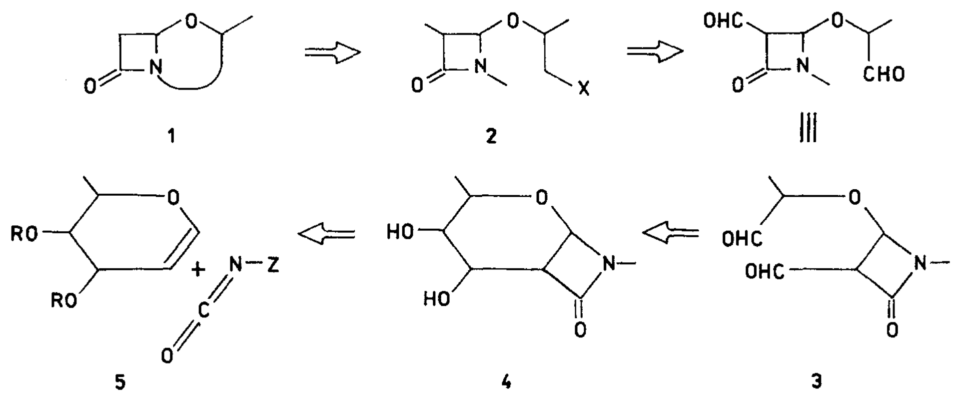
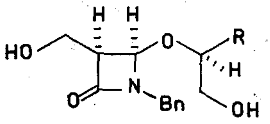
Abstract - *N*-Protected 2-*C*:1-*N*-carbonyl-2-deoxy-glycopyranosylamines **12**, **13**, and **16** were subjected to the two-step oxidation to afford dicarboxylic acids **20**, **21**, and **30**. Decarboxylation of the group located in a malonyl system with the β-lactam carbonyl group failed to give 1,4-disubstituted azetidinones. Bromides **45**, **46**, obtained from **30** by standard transformations, subjected to fluoride-anion-induced cyclization, failed to form clavam **53**.

Several years ago we have initiated a synthetic project leading from sugars to 1-oxabicyclic β-lactams **1** (Scheme 1).[1,2] This has prompted us to investigate the [2+2]cycloaddition of isocyanates to glycals **5** [3,4,5] and glycolic cleavage of the *vic* diol grouping present in sugar β-lactams **4**.[6,7] This cleavage produces reactive dialdehyde **3** which easily undergoes the intramolecular aldol reaction. Reduction of dialdehydes with sodium borohydride has been found to give 3,4-disubstituted azetidinones **6** - **8** which could be potential precursors of 1-oxabicyclic β-lactam antibiotics **1**.[6,7,8]

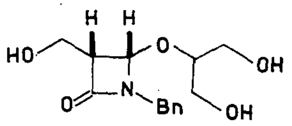
Scheme 1



Stereocontrolled transformation of compounds **5** into bicyclic β-lactams **1** requires not only specificity of cycloaddition, but also protection of chirality at the carbon atom stemming from C-5 of the glycal molecule. The reduction of dialdehydes **3** to the respective alcohols has a disadvantage involving to the loss of chirality at that carbon atom, owing to formation of two geminal hydroxymethyl groups in compounds 7 and **8**. This drawback can be prevented by oxidation of dialdehydes 3 to the respective dicarboxylic acids. In this paper we describe the oxidation of dialdehydes 3 and the consequences of this reaction for the subsequent transformation of 3 into the clavam (7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane) skeleton.



6 : R = H
7 : R = CH_2OH



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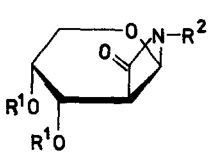
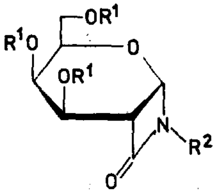
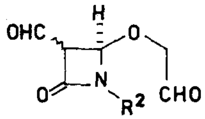


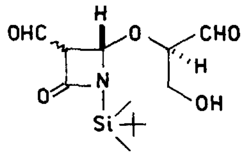
9 : R^1=Bn, R^2=H
10 : R^1=R^2=Bn
11 : R^1=Bn, R^2 Si
12 : R^1=H, R^2=Bn
13 : R^1=H, R^2=Si



14 : R^1=Bn, R^2=H
15 : R^1=Bn, R^2=Si
16 : R^1=H, R^2 = Si



17 : R^2=Bn
18 : R^2=Si



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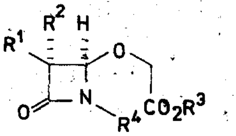
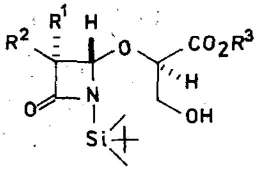


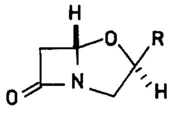
20 : R^1=CO_2H, R^2=R^3=H, R^4=Bn
21 : R^1=CO_2H, R^2=R^3=H, R^4=Si
22 : R^1=R^3=H, R^2=CO_2H, R^4=Bn
23 : R^1=R^3=H, R^2=CO_2H, R^4=Si
24 : R^1=CO_2CH_3, R^2=H, R^3=CH_3, R^4=Bn
25 : R^1=CO_2CHPh_2, R^2=H, R^3=$CHPh_2$, R^4 = Bn
26 : R^1=CO_2CHPh_2, R^2=H, R^3=$CHPh_2$, R^4=Si
27 : R^1=H, R^2=CO_2CH_3, R^3=CH_3, R^4=Bn
28 : R^1=H, R^2=CO_2CHPh_2, R^3=$CHPh_2$, R^4=Bn
29 : R^1 =H, R^2=CO_2CHPh_2, R^3=$CHPh_2$, R^4= Si



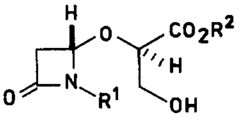
30 : R^1=CO_2H, R^2=R^3=H
31 : R^1=R^3=H, R^2=CO_2H
32 : R^1=CO_2CH_3, R^2=H, R^3=CH_3
33 : R^1=CO_2CHPh_2, R^2=H, R^3=$CHPh_2$
34 : R^1=H, R^2=CO_2CH_3, R^3=CH_3
35 : R^1=H, R^2=CO_2CHPh_2, R^3=$CHPh_2$
36 : R^1=H, R^2=CO_2Allyl, R^3=Allyl

RESULTS AND DISCUSSION

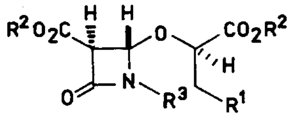
For the present study we selected the known N-benzylated compound **12** and two N-tertbutyldimethylsilyl-substituted β-lactams **13** and **16**. Compounds **12**, **13**, and **16** were obtained from compound **9** and **14** respectively, *via* appropriate protection of the nitrogen atom followed by hydrogenolysis of benzyl ethers.



37 : R = $CH_2CH(NH_2)CO_2H$
38 : R = CH_2CH_2OH
39 : R = CH_2OH
40 : R = CO_2H
41 : R = CH_2CO_2H



42: R^1=Si+ , R^2=H
43: R^1=H , R^2=CH_3



44: R^1=OMs , R^2=CH_3, R^3=Si+
45: R^1=Br, R^2=CH_3, R^3=Si+
46: R^1=Br, R^2=$CHPh_2$, R^3=Si+
47: R^1=Br, R^2=CH_3, R^3=H

Compounds **12**, **13**, and **16** were subjected for the glycolic cleavage in the presence of phosphate buffer to afford the respective dialdehydes **17**, **18** and **19**, which without isolation were oxidized with sodium chlorite, in the presence of hydrogen peroxide as a chlorine scavenger,[9] to afford dicarboxylic acids in a good yield. We found this known method[9] to be very convenient, proceeding without affecting the β-lactam ring and allowing for configuration control at C-3 of the azetidinone ring. Owing to the β-dicarbonyl grouping present in compounds **17**, **18**, and **19**, epimerization at C-3 is fairly easy. When the dialdehydes were oxidized below -5 °C, the *cis* configuration at C-3 and C-4 of the azetidinone ring was preserved (**20**, **21**, and **30**), whereas oxidation at room temperature led to trans isomers (**22**, **23**, and **31**). Crude acids **20-23**, and **31** were esterified with diazomethane or diazodiphenylmethane, and were characterized as the respective diesters **24-29** and **32-35**; the *cis* and *trans* configuration of the azetidinone rings were proved by ^1H NMR and confirmed by X-ray analysis (cf. Experimental).

Upon purification by chromatography, *cis* diesters **25**, **26**, **32**, and **33** underwent partial isomerization, whereas **24** was completely epimerized.

Acids **30** and **31** represent very attractive starting materials for stereocontrolled synthesis of the recently discovered new clavam antibiotics **37**[9], **38**[10], and **39**-**41**[11].

Decarboxylation of the group located in a malonyl system with the β-lactam carbonyl group in compound **30** should produce 1,4-disubstituted azetidinone **42**. C-N bond formation between the hydroxymethyl group and the nitrogen atom in compound **42** should afford the bicyclic skeleton of antibiotics **39**-**41**. The racemic compound **43** related to **42** has been obtained by condensation of 4-acetoxyazetidinone-2 with glyceric acid ester.[12] The two-step formation of **43** has been found to involve displacement of the hydroxy group by a bromide atom, followed by cyclization using a silver complex[12]. Similar approaches to clavams have been reported, for example, by Hoppe and Hilpert[13], and by the Hoffmann- la Roche group.[14,15]

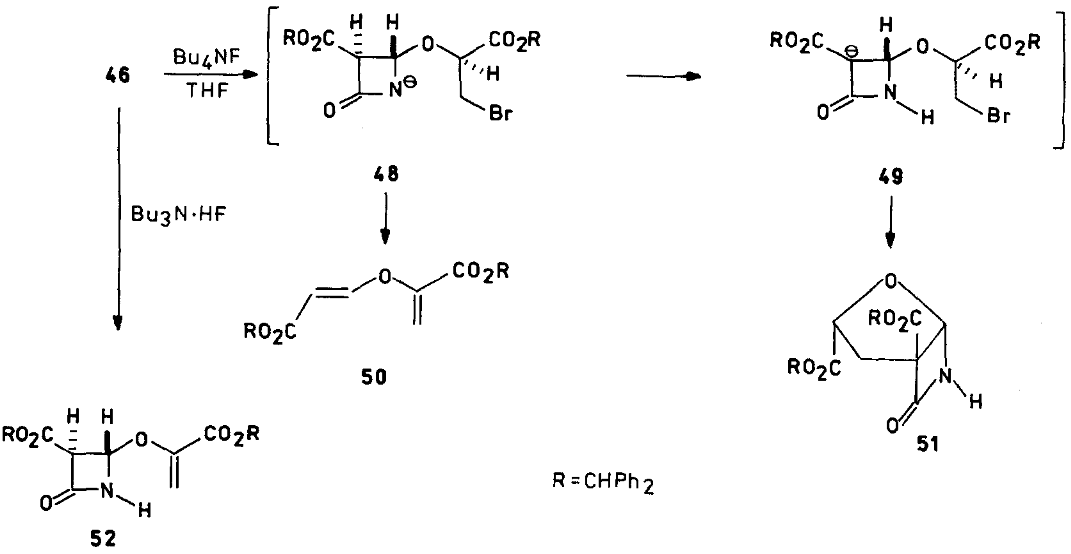
Discrimination of both carboxylic functions in **30**, and decarboxylation of that at C-3 of the azetidinone ring were very substantial for the idea shown in Scheme 1; not only **37** - **41**, but all natural clavams have no substituent at C-6 (C-3 of the azetidinone-2 ring).[9,10,11,16] However, numerous carefully performed experiments failed, so far, to afford decarboxylation of **30**. We found that the crude diacid **30** which easily epimerized to **31**, was stable up to about 100°C (in polar, and not polar solvents, and in the presence of sodium cations [17,18]). Temperature elevation above 100°C caused decomposition of the substrate. Tsuji[19] palladium-catalyzed decarboxylation of diallyl ester **36** also failed to give deprotection of both carboxylic functions.

Because of the failure of the decarboxylation experiments, we resolved to examine, at the stage of diesters **34** and **35**, the formation of the five-membered ring of the clavam skeleton. Having silyl protection at the nitrogen atom, we directed attention to fluoride-anion-induced cyclization.[20] Diesters **34** and **35** were transformed into bromides **45** and **46** respectively, *via* the mesyl stage **44**, or by the carbon tetrabromide - triphenylphosphine procedure.[21] The structure of product **45** was confirmed by X-ray crystallography, thus also proving, the structure and configuration of related *cis* and *trans* azetidinones **20**-**36** (cf. Experimental).

We attempted cyclization of **45** and **46** using anhydrous tetrabutylammonium fluoride[22]. Treatment of **46** with pure anhydrous Bu_4NF in THF led to formation of two products **50** and **51** (Scheme 2). The fluoride anion generates the heteroanion **48**, which can abstract the malonyl proton from C-3 of the azetidinone ring to afford the carbanion **49**, or can eliminate the isocyanate anion and a HBr molecule to give divinyl ether derivative **50**; the *vicinal* coupling constant between olefinic protons in **50** amounting to 3.0 Hz testifies to E configuration of the double bond,[23] suggesting a concerted retro [2+2]cycloaddition. The carbanion **49** can be intramolecularly alkylated to afford the bicyclic compound **51**. Contamination of Bu_4NF with Bu_3NHF caused deprotection of the nitrogen atom and β-elimination of hydrogen bromide from the side chain of **46**, yielding the respective unsaturated ester **52** in 30% yield.

Treatment of **46** with cesium fluoride in acetonitrile afforded compound **50** and a mixture of two geometric isomers **54**. The enamine structure of **54**, in which one amino proton formed a chelate with the ester carbonyl group, was proved by comparison of its ^{1}H NMR spectral data with the respective data of structurally related Z and E enaminosulfoxides[23] 55 and 56. Coupling constants of amino protons $^{3}J_{syn}$= 7.9 and $^{3}J_{anti}$= 12.8 Hz, found in 55 and 56, respectively, are similar to those characteristic of 54. The presence of 54 in the reaction mixture proves intermediate formation of the expected compound 53 which is, however, unstable, owing to angle strains and relative location of the functional groups, and undergoes β-elimination of the alkoxy group, followed by the opening of the four-membered ring by a hydroxyl, and subsequent β-elimination of the amino function to produce 54 (Scheme 3).

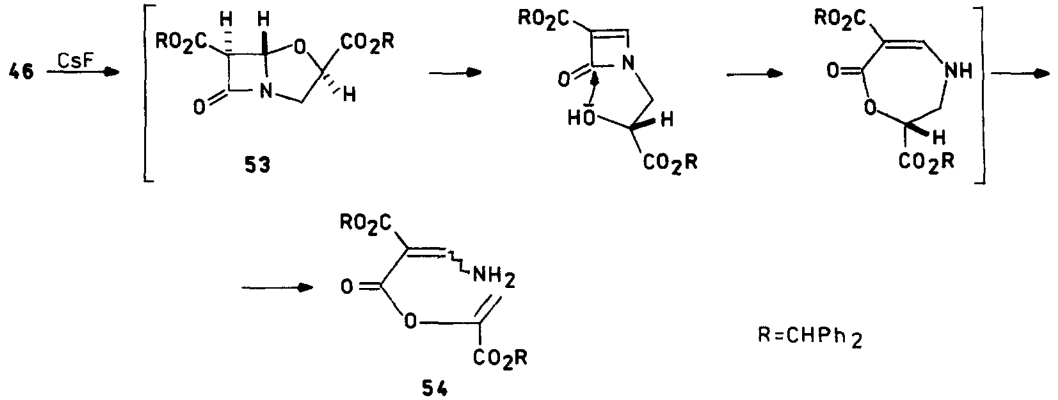
Scheme 2

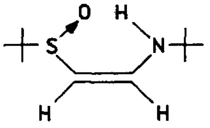


Cyclization of desilylated diester 47 using AgFOD,[15] which could produce the clavam 53, led to decomposition of the substrate. Among the products, the compound 52 and unidentified destructs having an enamino fragment were found in the ^{1}H NMR spectrum of the post-reaction mixture.

Location of the alkoxycarbonyl function at the C-6 carbon atom of the clavam skeleton in 53 destabilizes the bicyclic system and promotes its rearrangement *via* β-elimination processes.

Scheme 3





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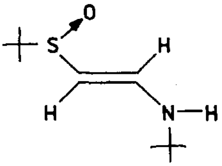

56

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were recorded with a Beckman 4240 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were taken with Varian Gemini 200 and Brucker AM 500 spectrometers. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

X ray structure determination of 45.

A crystal of 45 from a hexane-ethyl acetate mixture was used for data collection at a four-circle CAD4 diffractometer. Systematic extinctions showed the $P2_12_12_1$ space group. Unit cell parameters obtained by the centering procedure of 25 reflections are: a=8.068(2), b=11.246(1), c=22.767(5) Å, V=2066.8(7) Å^3, Z=4, D_{calc}= 1.316 g.cm^{-3}. A total of 2624 reflections were measured using CuK$_\alpha$ radiation and the $\Theta/2\Theta$ scan technique, within Θ range of 0-78°. Intensities were corrected for Lorentz polarization and fluctuation of intensities of three control reflections (loss of 2%). 2340 Reflections with $F>1\sigma$ were used for structure solution and refinement.

The structure was solved by direct methods (SHELXS) and was refined with anisotropic thermal parameters by full-matrix least-squares procedure to R= 0.0554, R_w= 0.0570 (w=

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The structure was solved by direct methods (SHELXS) and was refined with anisotropic thermal parameters by full-matrix least-squares procedure to R= 0.0554, R_w= 0.0570 ($w= 1/\sigma_F{}^2$). After refinement with isotropic temperature factors for the heavy atoms, and calculated positions for H-atoms, reflections were additionally corrected by empirical absorption factor using the DIFABS program (minimum and maximum corrections were 0.649 and 1.502, respectively). Final difference maps showed electron density fluctuations not exceeding 0.25 e/Å^3, and maximum shift/error ratio during final cycle of refinement was below 10%.

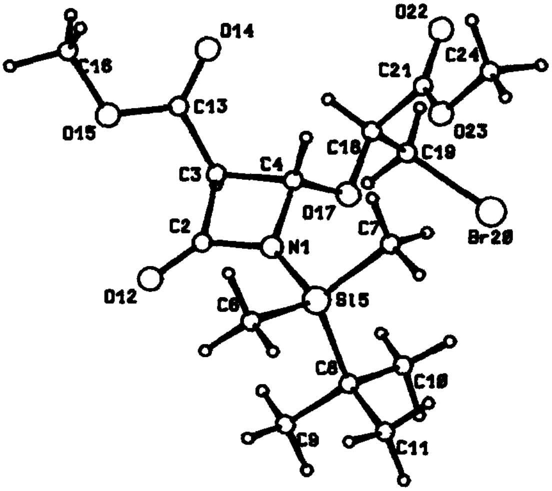

Fig.1 Pluto diagram of compound 45

Tables 1 and 2 show refined atomic coordinates and geometry of the molecule. X-ray analysis of 45 confirms trans configuration at the C3-C4 bond of β-lactam [C13-C4-C3-O17 angle -123.7(6)°] (see also Fig. 1). Four-membered ring is almost planar, with intracyclic torsion angles do not exceeding 3(1)°, and carbonyl oxygen, and Si15 nearly coplanar [O12-C2-N1-Si15 angle -11(1)°]. Configuration at C18 carbon is S.

Table 1. Fractional atomic coordinates with e.s.d.'s in parentheses for non-hydrogen atoms

	x/a	y/b	z/c
N1	7099(7)	3120(4)	3128(2)
C2	5950(9)	3217(6)	2687(3)
C3	6482(8)	2045(6)	2402(3)
C4	7823(8)	2016(5)	2890(3)
SI5	7840(2)	4124(2)	3675(1)
C6	766(1)	5666(6)	3380(4)
C7	10049(9)	3715(7)	3795(4)
C8	652(1)	3916(8)	4351(4)
C9	470(1)	416(1)	4207(4)
C10	666(1)	260(1)	4587(4)
C11	717(2)	486(1)	4821(5)
O12	4936(7)	3974(5)	2579(2)
C13	711(1)	1997(6)	1791(3)
O14	8349(9)	1462(6)	1643(3)
O15	6165(6)	2603(5)	1418(2)
C16	671(1)	2584(8)	811(4)
O17	7661(5)	1095(4)	3309(2)
C18	8359(9)	8(5)	3106(3)
C19	7598(9)	-1019(7)	3456(3)
BR20	8084(1)	-918(1)	4284(0)
C21	10228(9)	-58(6)	3144(3)
O22	10942(7)	-895(5)	2947(3)
O23	10918(6)	869(5)	3398(3)
C24	12722(9)	84(1)	3440(4)

Table 2. Interatomic distances (Å) and bond angles (°) for non-hydroge atoms

Atoms	*Bond*	*Atoms*	*Bond*
C2 - N1	1.371(9)	C10 - C8	1.57(1)
C4 - N1	1.475(8)	C11 - C8	1.59(1)
SI5 - N1	1.785(5)	O14 - C13	1.21(1)
C3 - C2	1.53(1)	O15 - C13	1.332(9)
O12 - C2	1.206(9)	C16 - O15	1.45(1)
C4 - C3	1.552(9)	C18 - O17	1.423(7)
C13 - C3	1.48(1)	C19 - C18	1.53(1)
O17 - C4	1.415(8)	C21 - C18	1.51(1)
C6 - SI5	1.866(7)	BR20 - C19	1.930(7)
C7 - SI5	1.861(8)	O22 - C21	1.191(9)
C8 - SI5	1.889(9)	O23 - C21	1.316(9)
C9 - C8	1.52(1)	C24 - O23	1.459(9)

Atoms	*Angle*	*Atoms*	*Angle*
N1 - C2 - C3	93.0(5)	C6 - SI5 - C8	111.3(4)
N1 - C2 - O12	131.6(6)	C7 - SI5 - C8	113.0(4)
C2 - N1 - C4	93.8(5)	SI5 - C8 - C9	110.2(6)
C2 - N1 - SI5	133.4(4)	SI5 - C8 - C10	110.6(6)
N1 - C4 - C3	88.3(5)	SI5 - C8 - C11	106.2(6)
N1 - C4 - O17	109.4(5)	C9 - C8 - C10	108.3(8)
C4 - N1 - SI5	131.0(4)	C9 - C8 - C11	109.8(8)
N1 - SI5 - C6	108.1(3)	C10 - C8 - C11	111.7(8)
N1 - SI5 - C7	105.5(3)	O14 - C13 - O15	123.3(7)
N1 - SI5 - C8	107.5(3)	C13 - O15 - C16	115.1(6)
C2 - C3 - C4	84.8(5)	O17 - C18 - C19	108.7(5)
C2 - C3 - C13	121.7(6)	O17 - C18 - C21	114.7(5)
C3 - C2 - O12	135.4(6)	C18 - C19 - BR20	112.5(5)
C3 - C4 - O17	115.7(5)	C19 - C18 - C21	109.4(5)
C4 - C3 - C13	115.6(6)	C18 - C21 - O22	120.0(6)
C3 - C13 - O14	124.2(7)	C18 - C21 - O23	114.1(6)
C3 - C13 - O15	112.4(6)	O22 - C21 - O23	125.9(7)
C4 - O17 - C18	111.9(5)	C21 - O23 - C24	115.8(7)
C6 - SI5 - C7	111.0(4)		

Compound **9** was obtained from 3,4-di-O-benzyl-D-arabinal[25] and trichloroacetyl isocyanate[5] analogically as described for **14**.[6]

***N*-Benzyl-3,4-di-O-benzyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine** (**10**). Compound **9** (0.68 g, 2.0 mmol) in benzene (25 mL) was treated with benzyl chloride (1.2 mL, 10.4 mmol), K_2CO_3 (4 g) and tetrabutylammonium bromide (0.1 g). The mixture was stirred under reflux for 3 h, filtered, washed with water, dried, and evaporated. The residue was purified on a silica gel column to give **10** (0.56 g, 66%); mp 58-60°C; $[\alpha]_D$ -65.2° (*c* 1, CH_2Cl_2); IR (KBr): 1750 cm^{-1}; ^1H NMR ($CDCl_3$): 3.39 (dd, 1H, J_{12}= 4.4, J_{23}= 5.4 Hz, H-2), 3.50 (dd, 1H, J_{45}= 2.5, $J_{55'}$= 12.0 Hz, H-5), 3.72 (m, 1H, H-4), 3.84 (dd, 1H, $J_{45'}$= 4.5 Hz, H-5'), 3.90(dd, 1H, J_{34}= 3.2 Hz, H-3), 4.21, 4.45 (2d, 2H, J= 14.9 Hz, benzyl), 4.64, 4.78 (2d, 2H, J= 12.4 Hz, benzyl) 4.66 (s, 2H, benzyl), 5.21 (d, 1H, H-1); Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.49; H, 6.35; N, 3.26. Found: C, 75.4; H, 6.5; N, 3.3.

3,4-Di-O-benzyl-*N*-t-butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine (11). - Compound **9** (1.02 g, 3.0 mmol) in anhydrous dimethylformamide (10 mL) was treated with t-butyldimethylsilyl chloride (0.54 g, 3.6 mmol) and 4-*N,N*-dimethylaminopyridine (0.44 g, 3.6 mmol). The mixture was stirred at room temp. for 16 h under nitrogen, poured into water, and extracted with hexane. The extract was dried, evaporated, and purified on a silica gel column to give **11** (1.15 g, 84%); $[\alpha]_D$ - 67.5° (*c* 1, CH_2Cl_2); IR (film) : 1770 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.23, 0.25, 0.94 (3s, 15 H, t-$BuMe_2Si$), 3.54 (dd, 1H, J_{12}= 4.6, J_{23}= 5.5 Hz, H-2), 3.67-3.97 (m, 4H, H-3, 4, 5, 5'), 4.63, 4.80 (2d, 2H, J= 12.2 Hz, benzyl), 4.72 (s, 2H, benzyl), 5.31 (d, 1H, H-1); Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 69.0; H, 7.7; N, 3.0.

3,4,6-Tri-*O*-benzyl-*N*-t-butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine (**15**). - Compound **15** was obtained by the method described above, 86%; $[\alpha]_D$ +22.6° (*c* 1, CH_2Cl_2); IR (film): 1760 cm^{-1}; ^1H NMR ($CDCl_3$): 0.24, 0.26, 0.95 (3 s, 15H, t-$BuMe_2Si$), 3.45-3.59 (m, 3H, H-2, 6, 6'), 3.81 (bdd, 1H, J_{56}= 5.7, $J_{56'}$= 7.5 Hz, H-5), 3.88 (dd, 1H, J_{23}= 5.4, J_{34}= 3.1 Hz, H-3), 3.91 (bd, 1H, H-4), 4.34, 4.41 (2d, 2H, J= 11.8 Hz, benzyl), 4.62, 4.86 (2 d, 2H, J= 12.1 Hz, benzyl), 4.63, 4.95 (2d, 2H, J= 11.7 Hz, benzyl), 5.42 (d, 1H, J_{12}= 4.8 Hz, H-1); Anal. Calcd for $C_{34}H_{43}NO_5Si$: C, 71.17; H, 7.55; N, 2.44. Found: C, 71.1; H, 7.5; N, 2.3.

***N*-Benzyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine** (**12**). - Compound **10** (0.86 g, 2 mmol) in ethyl acetate (18 mL) was shaken at room temp. in the presence of 5% Pd/C under hydrogen (1 atm) for 16 h. Subsequently the mixture was filtered and the solvent was evaporated to afford **12** (0.46 g, 93%) identical with the compound obtained previously[6].

***N*-t-Butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine** (**13**). - Compound **13** was obtained according to the procedure described for compound **12**: 92%; mp 67-69°C; $[\alpha]_D$ -81.1° (*c* 1, MeOH); IR (KBr): 1750, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): 0.25, 0.95 (2s, 15H, t-$BuMe_2Si$), 3.36 (t, 1H, J_{12}= 4.5, J_{23}= 4.0 Hz, H-2), 3.82 (m, 2H, H-5,5'), 3.93 (q, 1H, Σ J= 11.3 Hz, H-4), 4.16 (t, 1H, J_{34}= 4.0 Hz, H-3), 5.32 (d, 1H, H-1). Anal. Calcd for $C_{12}H_{23}NO_4Si$: C, 52.72; H, 8.48; N, 5.12. Found: C, 52.3; H, 8.7; N, 5.1.

***N*-t-Butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine** (16). - Compound **16** was obtained according to the procedure described for compound **12**; 96%; mp 109-111°C; $[\alpha]_D$ +78.5° (*c* 1, MeOH); IR (KBr) 1740 cm^{-1}; ^1H NMR (acetone-d_6): 0.26, 0.96 (2s, 15H, t-BuMe_2Si), 3.24 (t, 1H, J_{12}= 4.7, J_{23}= 4.7 Hz, H-2), 3.64-3.82 (m, 3H, H-5, 6, 6'), 3.93 (d, 1H, J_{34}= 3.9 Hz, H-4), 3.99 (t, 1H, H-3), 5.47 (d, 1H, H-1); Anal. Calcd for $C_{13}H_{25}NO_5Si$: C, 51.46; H, 8.34; N, 4.62. Found: C, 51.8; H, 8.6; N, 4.2.

General procedure for glycolic cleavage. Compound **12, 13** or **16** (2.0 mmol) was dissolved in t-butanol (8 mL) and 8% of $NH_4H_2PO_4$ (28 mL), cooled to -5°C, and treated with $NaIO_4$ (0.46 g, 2.2 mmol in 3 mL of water). After 20 min. 35% hydrogen peroxide (0.4 mL) and sodium chlorite (0.64 g, 7.1 mmol) in (5 mL) water were added slowly. Stirring and cooling were maintained for additional 30 min. The excess of oxidants was decomposed with sodium bisulfite; the product was salted out with ammonium sulfate, and extracted with ethyl acetate. The extract was dried and evaporated to afford the free acid **20, 21** or **30**. Crude acids were subsequently esterified with diazomethane or diazodiphenylmethane in an ethyl ether - methanol solution and purified on silica gel to give **25, 26, 32** or **33** in 70-90% yield.

Oxidation of **12, 13**, or **16** at room temperature, followed by standard esterification with diazomethane or diphenyldiazomethane in an ethyl ether solution, gave trans isomers **27-29, 34**, and **35** respectively

(3S, 4R) 1-Benzyl-3-diphenyl-methoxycarbonyl-4-(diphenymethoxycarbonyl)methoxyazedinone-2 (25) : 62%; mp 109-110°; $[\alpha]_D$ +31.5° (c 0.8, CH_2Cl_2); IR (film) : 1745, 1790 cm^{-1}; ^1H NMR ($CDCl_3$) : 3.77, 3.88, (2d, 2H, J=17.1 Hz, OCH_2), 4.17 (d, 1H, J_{34}= 4.1 Hz, H-3), 4.35, 4.56 (2d, 2H, J= 15.2 Hz benzyl) 5.06 (d, 1H, H-4), 6.89, 6.92 (2s, 2H, $2CHPh_2$); Anal. Calcd for $C_{39}H_{33}NO_6$: C, 76.57; H, 5.44; N, 2.29. Found: C, 76.2; H, 5.3; N, 2.4.

(3S, 4R) 1-t-Butyldimethylsilyl-3-diphenylmethoxycarbonyl-4-(diphenylmethoxycarbonyl)methoxy-azetidinone-2 (26): ^1H NMR ($CDCl_3$) signals taken from the spectrum of a mixture of compounds **26** and **29**: 0.25, 0.30, 0.94 (3s, 15H, t-BuMe_2Si), 3.79, 3.97 (2d, 2H, J= 16.9 Hz, OCH_2), 4.24 (d, 1H, J_{34}= 4.0 Hz, H-3), 5.16 (d, 1H, H-4).

(3R, 4S, 1'R) 1-t-Butyldimethylsilyl-3-methoxycarbonyl-4-(1'-methoxycarbonyl-2'-hydroxy)ethoxy-azetidinone-2 (32) : 86%; $[\alpha]_D$ +56.0° (*c* 0.75, CH_2Cl_2); IR (film) : 1740, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.22, 0.23, 0.89 (3s, 15H, t-BuMe_2Si) 3.67-3.73 (m, 2H, CH_2OH), 3.67, 3.70 (2s, 6H, $2OCH_3$), 4.12 (dd, 1H, J= 3.4, 6.3 Hz, OCH), 4.16 (d, 1H, J_{34}= 4.1 Hz, H-3), 5.21 (d, 1H, H-4). Anal. Calcd for $C_{15}H_{27}NO_7Si$: C, 49.83; H, 7.54; N, 3.88. Found: C, 49.8; H, 7.7; N, 4.0.

(3R, 4S, 1'R) 1-t-Butyldimethylsilyl-3-diphenylmethoxycarbonyl-4-(1'-diphenylmethoxycarbonyl-2'-hydroxy)ethoxy-azetidinone-2 (33) : 69%; $[\alpha]_D$ +48.3° (*c* 1.4, CH_2Cl_2); IR (film) : 1740, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.22, 0.29, 0.94 (3s, 15H, t-BuMeSi), 3.34

(ddd, 1H, J= 3.0, 6.4, and 12.1 Hz, CH_aH_bOH), 3.46 (ddd, 1H, J= 5.5, 7.8, and 12.1 Hz, CH_aH_bOH), 4.15 (dd, 1H, J= 3.0 and 5.5 Hz, OCH), 4.29 (d, 1H, J_{34}= 4.1 Hz, H-3), 5.24 (d, 1H, H-4), 6.86, 6.93 (2s, 2H, $2CHPh_2$). Anal. Calcd for $C_{39}H_{42}NO_7Si$: C, 70.33; H, 6.52; N, 2.10. Found: C, 69.6; H, 6.3; N, 2.4.

(3R, 4R) 1-Benzyl-3-methoxycarbonyl-4-(methoxycarbonyl)methoxy-azetidinone-2 (27) : 81%; $[\alpha]_D$ -92.7° (*c* 1.2, CH_2Cl_2); IR (film) : 1745, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) : 3.64, 3.70 (2s, 6H, $2OCH_3$); 3.88, 4.04 (2d, 2H, J= 16.6 Hz, OCH_2), 3.99 (t, 1H, J_{34}= 1.2 and 0.7 Hz, H-3), 4.18, 4.61 (2d, 2H, J= 15.2 Hz, benzyl), 4.99 (d, 1H, H-4). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.59; N, 4.56. Found: C, 58.4; H, 5.6; N, 4.5.

(3R, 4R) 1-Benzyl-3-diphenylmethoxycarbonyl-4-(diphenylmethoxycarbonyl)methoxy-azetidinone-2 (28) : 66%; $[\alpha]_D$ -61.9° (*c* 1.2, CH_2Cl_2) : IR (film) : 1735, 1755, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) : 4.04, 4.14 (2d, 2H, J= 16.5 Hz, OCH_2), 4.13 (t, 1H, J_{34}= 1.1 and 0.7 Hz, H-3), 4.19 (dd, 1H, J = 15.2 and 0.7 Hz, benzyl), 4.65 (d, 1H, benzyl), 5.06 (d, 1H, H-4), 6.86, 6.89 (2s, 2H, $2CHPh_2$). Anal. Calcd for $C_{39}H_{33}NO_6$: C, 76.57; H, 5.45; N, 2.29. Found: C, 76.2; H, 5.6; N, 2.1.

(3R, 4R) 1-t-Butyldimethylsilyl-3-diphenyl-methoxycarbonyl-4-(diphenylmethoxycarbonyl)methoxy-azetidinone-2 (29): 59%; $[\alpha]_D$ +16.7°C (c 1, CH_2Cl_2): IR (film): 1780, 1750 cm^{-1}; ^1H NMR ($CDCl_3$): 0.24, 0.25, 0.93 (3s, 15H, t-$BuMe_2Si$), 4.17 (d, 1H, J_{34}= 1.3 Hz, H-3), 4.25 (d, 2H, OCH_2), 5.15 (d, 1H, H-4), 6.85, 6.91 (2s, 2H, $2CHPh_2$); Anal. Calcd for $C_{38}H_{41}NO_6Si$: C, 71.77; H, 6.51; N, 2.20. Found: C, 17.2; H, 6.7; N, 2.0.

(3S, 4S, 1'R) 1-t-Butyldimethylsilyl-3-methoxycarbonyl-4-(1'-methoxycarbonyl-2'-hydroxy)ethoxy-azetidinone-2 (34) : 70%; $[\alpha]_D$ +18.9° (*c* 1.25, CH_2Cl_2); IR (film) : 1740, 1765, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.32, 0.34, 0.99 (3s, 15H, t-$BuMe_2Si$), 3.77, 3.79 (2s, 6H, $2OCH_3$), 3.85, 3.93 (2 m, 2H, CH_2OH) 3.90 (d, 1H, J_{34}= 1.2 Hz, H-3), 4.08 (dd, 1H, J= 3.6 and 6.1 Hz, OCH), 5.29 (d, 1H, H-4). Anal. Calcd for $C_{15}H_{27}NO_7Si$: C, 49.83; H, 7.54; N, 3.88. Found: C, 49.7; H, 7.6; N, 3.8.

(3S, 4S, 1'R) 1-t-Butyldimethylsilyl-3-diphenylmethoxycarbonyl-4-(1'-diphenylmethoxycarbonyl-2'-hydroxy)ethoxy-azetidinone-2 (35) : 56%; $[\alpha]_D$ +14.6° (*c* 1.3, CH_2Cl_2); IR (film) : 1735, 1750, 1765, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.14, 0.15, 0.81 (3s, 15H, t-$BuMe_2Si$), 3.79 (dd, 1H, J= 6.2 and 11.8 Hz, CH_aH_bOH), 3.87 (dd, 1H, J= 3.5 and 11.8 Hz, CH_aH_bOH), 3.92 (d, 1H, J_{34}= 1.2 Hz, H-3), 4.09 (dd, 1H, J= 6.2 and 3.5 Hz, OCH), 5.20 (d, 1H, H-4), 6.79, 6.86 (2s, 2H, $2CHPh_2$). Anal. Calcd for $C_{39}H_{42}NO_7Si$: C, 70.33; H, 6.52; N, 2.10. Found: C, 69.9; H, 6.5; N, 2.3.

(3R, 4R) 1-Benzyl-3-allyloxy-carbonyl-4-(allyloxycarbonyl)methoxy-azetidinone-2 (36). Crude compound 20 (84 mg, 0.3 mmol) was dissolved in anhydr. THF (2 mL) and treated with *N,N*-disopropyl-O-allyl-isourea. The mixture was stirred for 20 h at 40°C. Subsequently the solvent was evaporated and the crude mixture was purified by chromatography to give (70 mg, 64%); colorless oil; $[\alpha]_D$ - 80.3° (*c* 1, CH_2Cl_2); IR (film): 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 3.98, 4.14 (2d, 2H, J= 16.6 Hz, OCH_2), 4.09 (bs, 1H, H-3), 4.25, 4.70 (2d, 2H, J= 15.4 Hz, benzyl), 4.52-4.76 (m, 4H, allyl), 5.08 (d, 1H,

J_{34}= 1.1 Hz, H-4), 5.22-5.40, 5.76-6.02 (2m, 6H, 2 allyl); Anal. Calcd for $C_{13}H_{13}O_6N$: C, 63.49; H, 5.90; N, 3.90. Found: C, 62.9; H,6.0; N, 3.8.

(3S, 4S, 1'R) 1-t-Butyldimethylsilyl-3-methoxycarbonyl-4-(1'-methoxycarbonyl-2'-mesyloxy)ethoxy-azetidinone-2 (44). Compound 32 (0.36 g, 1 mmol) in anhydrous pyridine (6 mL) was cooled to 0°C, and trated with mesyl chloride (0.17 g, 1.5 mmol). The mixture was left at room temp. for 2 h. Subsequently it was poured into cold water and extracted with chloroform. The extract was dried and evaporated. The crude residue was purified by chromatography to give **44**: (0.30 g, 69%); $[\alpha]_D$ +11.9° (*c* 1.25, CH_2Cl_2); IR ($CHCl_3$) : 1780, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) : 0.31, 0.32, 0.98 (3s, 15H, t-BuMe_2Si), 3.06 (s, 3H, CH_3SO_2), 3.78, 3.82 (2s, 6H, 2OCH_3), 3.94 (d, 1H, J_{34}= 1.3, H-3), 4.29 (dd, 1H, J= 2.9, 7.0 Hz, H-1'), 4.38 (dd, 1H, J= 7.0, 11.2 Hz, H-2'a), 4.58 (dd, 1H, H-2'b), 5.30 (d, 1H, H-4). Anal. Calcd for $C_{16}H_{20}NO_9Si$: C, 43.78; H, 6.74; N, 3.20. Found: C, 44.0; H, 7.0; N, 3.0.

(3S, 4S, 1'R) 1-t-Butyldimethyl-3-methoxycarbonyl-4-(2'-bromo-1'-methoxycarbonyl)-ethoxy-azetidinone-2 (45). Compound (0.22 g, 0.5 mmol) was dissolved in HMPA (4 mL) and anhydr. THF (12 mL), and treated with anhyd. LiBr (86 mg, 1 mmol). The mixture was stirred overnight. Subsequently it was poured into cold water and extracted with ethyl ether. The extract was dried, evaporated and purified by chromatography to afford 45 (0.14 g, 40%); mp 96-98°C; $[\alpha]_D$ + 0.3° (*c* 0.8, CH_2Cl_2), I.R. (film): 1770, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) : 0.31, 0.32, 0.91 (3s, 15H, t-BuMe_2Si), 3.51 (dd, 1H, J= 6.7, 11.0 Hz, H-2'a), 3.60 (dd, 1H, J= 11.0, 3.7 Hz, H-2'b), 3.71, 3.74 (2s, 6H, 2 OCH_3), 3.96(d, 1H, J_{34}= 1.3 Hz, H-3), 4.16 (dd, 1H, H-1'), 5.21 (d, 1H, H-4); Anal. Calcd for $C_{15}H_{26}BrNO_6Si$: C, 42.45; H, 6.19; N, 3.30. Found: C, 42.6; H,6.4; N, 3.2.

(3S, 4S, 1'R) 1-t-Butyldimethylsilyl-3-diphenylmethoxycarbonyl-4-(2'-bromo-1'-diphenylmethoxycarbonyl)ethoxy-azetidinone-2 (46). Compound **33** (0.66 g, 1 mmol) in anhydr. pyridine (12 mL) was cooled to 0°C and treated with triphenylphosphine (0.79 g, 3 mmol) and carbon tetrabromide (0.50 g, 1.5 mmol) in pyridine (3 mL). The mixture was left for 40 min at 0°C. Subsequently toluene (50 mL) was added. The solution was washed with water and saturated $CuSO_4$, dried, evaporated, and purified by chromatography to give the bromide **46**, (0.50 g, 69%); mp 93-95°C; $[\alpha]_D$ +4.3° (*c* 1, CH_2Cl_2); IR (KBr): 1780, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) : 0.19, 0.20, 0.89 (3s, 15H, t-BuMe_2Si), 3.57 (dd, 1H, J= 6.7, 11.0 Hz, H-2'a), 3.64 (dd, 1H, J= 3.9, 11.0 Hz, H-2'b), 4.13 (d, 1H, J_{34}= 1.2 Hz, H-3), 4.29 (dd, 1H, H-1'), 5.24 (d, 1H, H-4), 6.87, 6.93 (2s, 2H, 2$CHPh_2$). Anal. Calcd for $C_{39}H_{42}O_6BrNSi$: C, 64.26; H, 5.81; N, 1.92. Found: C, 64.3; H, 5.8; N, 2.2.

Attempts at decarboxylation. - Crude diacid **30** (100 mg, 0.3 mmol) and NaCl (20 mg) were dissolved in dimethylsulfoxide (3 mL). The mixture was heated at 80-90°C for 30 min. Subsequently it was poured into water and extracted with ethyl acetate. The extract was dried and treated with an ether solution of diazomethane. After chromatography, dimethyl ester **32** was the only isolated compound (20%). Heating of the same mixture at 100-110°C for 15 min, followed by the same work up, led to decomposition of the substrate **30**.

Diacid **30** heated in boiling benzene for 1 hr, followed by esterification with diazomethane, gave 15% of the ester **32**; longer heating caused decomposition of **30**.

Tsuji[19] decarboxylation. - $Pd(Ph_3P)_4$ (12 mg, 0.01 mmol) in anhydr. THF (1 mL) was treated with formic acid (0.03 mL, 0.8 mmol) and Et_3N (0.14 mL, 1 mmol) in THF (0.5 mL). The mixture was stirred under argon at room temp. and a solution of diallyl ester **36** (72 mg, 0.2 mmol) in THF (0.5 mL) was slowly added. Stirring was continued for 1 h. Subsequently the mixture was filtered and treated with a diazomethane - ether solution until a stable yellow colour persisted. The solution was evaporated and the residue was persisted purified on a silica gel column to give dimethyl ester 27 (42 mg, 65%).

Attempts at cyclization. - Bromide **46** (0.15 g, 0.2 mmol) dissolved in anhydr. THF (5 mL) was cooled to -40°C and treated under argon with a solution of anhydrous tetrabutylammonium fluoride (0.22 mmol) in THF (0.22 mL of 1 M solution). Temperature was maintained for 15 min . Subsequently the solvent was evaporated and the residue was separated on a silica gel column, to give **E 2-diphenylmethoxycarbonylvinyl-1'-diphenylmethoxycarbonylvinyl ether (50)** (47 mg, 48%): IR (film): 1740, 1720, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): 5.32 (d, 1H, J= 2.8 Hz, H-2'a), 5.73 (d, 1H, $J_{1,2}$= 12.1 Hz, H-1), 5.97 (d, 1H, H-2'b), 6.94, 6.96 (2s, 2H, $2CHPh_2$), 7.61 (d, 1H, H-2); MS m/z: $M-(C_6H_5)_2CH$ = 323.3 and **(1S, 3R, 5S) 7-aza-3,5-di-(diphenylmethoxycarbonyl)-2-oxabicyclo[3.2.0]heptan-7-one (51)** (19 mg, ~20%): $[\alpha]_D$ -70.6° (*c* 0.5, CH_2Cl_2); IR (film): 3350, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 2.59 (dd, 1H, $J_{3,4}$= 9.6 and $J_{4,4'}$= 14.2 Hz, H-4), 2.99 (dd, 1H, $J_{3,4'}$= 1.2 Hz, H-4'), 4.97 (dd, 1H, H-3), 5.59 (s, 1H, H-1), 6.83, 6.89 (2s, 2H, $2CHPh_2$); Anal Calcd for $C_{33}H_{27}NO_6$: C, 74.27; H, 5.11; N, 2.63. Found: C, 74.0; H, 5.2; N, 2.5.

Reaction performed according to the procedure described above using decomposed tetrabutylammonium fluoride which contained Bu_3NHF at -70°C afforded **50** (40%) accompanied by **(3S, 4S) 3-diphenylmethoxycarbonyl-4-(1'-diphenylmethycarbonyl)vinyloxy-azetidinone -2 (52)** (37%); $[\alpha]_D$ -28.1° (*c* 1.1, CH_2Cl_2); IR (film): 3320, 1800, 1735, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): 4.18 (d, 1H, J = 0.9 Hz, H-3), 4.82 (d, 1H, J = 3.2 Hz, H-2'a), 5.61 (d, 1H, H-4), 5.63 (d, 1H, H-2'b), 6.60 (bs, 1H, NH), 6.92, 6.96 (2s, 2H, $2CHPh_2$); Anal. Calcd for $C_{33}H_{27}NO_6$: C, 74.27; H, 5.11; N, 2.63. Found: C, 74.0; H, 5.0; N, 2.6.

Bromide **46** (51 g, 0.07 mmol) dissolved in anhydrous acetonitrile (2 mL) was treated with anhydrous cesium fluoride (30 mg, 0.18 mmol) and stirred for 16 h at room temp under argon. Subsequently the mixture was filtered, evaporated and separated on a silica gel column to give **50** (11 mg, 33%), and **Z and E 1-amino-2-diphenylmethoxycarbonyl-2-(1'-diphenylmethoxycarbonyl)vinyloxycarbonyl-ethylene (54)** (6 mg, 16%); ^1H NMR ($CDCl_3$): 5.57 (d, 0.6 H, J = 1.6 Hz, H-2'a of the major isomer), 5.64 (d, 0.4 H, J = 1.7 Hz, H-2'a of the minor isomer), 5.75 (bs, 1H, NH), 6.18 (d, 0.4 H, H-2'b), 6.19 (d, 0.6 H, H-2'b), 6.91, 6.95 (2s, 2 x 0.6 H, $2CHPh_2$), 6.93, 6.98 (2s, 2 x 0.4H, 2 $CHPh_2$), 8.21 (dd, 0.6H, J = 8.4 and 15.5 Hz, H-1), 8.25 (dd, 0.4 H, J = 8.5 and 15.9 Hz, H-1), 8.63 (bd, 0.4 H, NH-chelate), 8.92 (bd, 0.6 H, NH-chelate).

(3S, 4S, 1'R) 3-Methoxycarbonyl-4-(2'-bromo-1'-methoxycarbonyl)-ethoxy-azetidinone-2

(47). Compound 45 (0.11 g, 0.25 mmol) dissolved in anhydr. CH_2Cl_2 (20 mL) was cooled to -70°C and treated, under argon, with a mixture of HF - pyridine - CH_2Cl_2 1:5:25 v/v (3.8 mL). This temperature was maintained for 30 min., whereupon it was allowed to rise to 0°, and the mixture was stirred for additional 2 h. Subsequently the solution was washed with water and saturated $CuSO_4$, dried, evaporated to dryness, and crystallized (ethyl acetate-hexane) to give 47 (67 mg, 86%); mp 104-106°C, $[\alpha]_D$ -40.2° (*c* 1, CH_2Cl_2) IR (film): (3340, 1765, 1750, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): 3.62 (dd, 1H, $J_{1'2'a}$ = 6.2, $J_{2'a2'b}$= 11.1 Hz, H-2a'), 3.70 (dd, 1H, $J_{1'2'b}$= 3.8 Hz, H-2'b), 3.80, 3.83 (2s, 6H, 2 x OCH_3), 4.06 (d, 1H, J_{34} = 1.3 Hz, H-3), 4.45 (dd, 1H, H-1'), 5.37 (d, 1H, H-4); Anal. Calcd for $C_9H_{12}BrNO_6$: C, 34.86; H, 3.88; N, 4.52. Found: C,35.1; H, 3.8; N, 4.6.

Cyclization of 47 using Ag FOD. Compound 47 (62 mg, 0.2 mmol) in anhydr DMF (4 mL) was cooled to 0°C under argon, and treated with AgFOD (0.16 g, 0.4 mmol). The mixture was stirred for 2 h at room temp. Subsequently it was filtered and evaporated. After partial purification on a silica gel column, the mixture of the products was investigated by ^1H NMR. Compound 52 ($R=CH_3$) was identified as the main component.

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