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SYNTHESIS OF α-(S)-ACYLAMINO-N-(HYDROXYDIOXOCYCLOBUTENYL)-γ-LACTAMS

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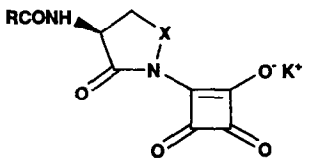
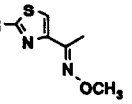
Abstract: Monocyclic γ- lactams **2**, activated by a hydroxycyclobutenedione moiety have been prepared from (L)-N-^{t}Boc-glutamine, as potential antibacterial agents.

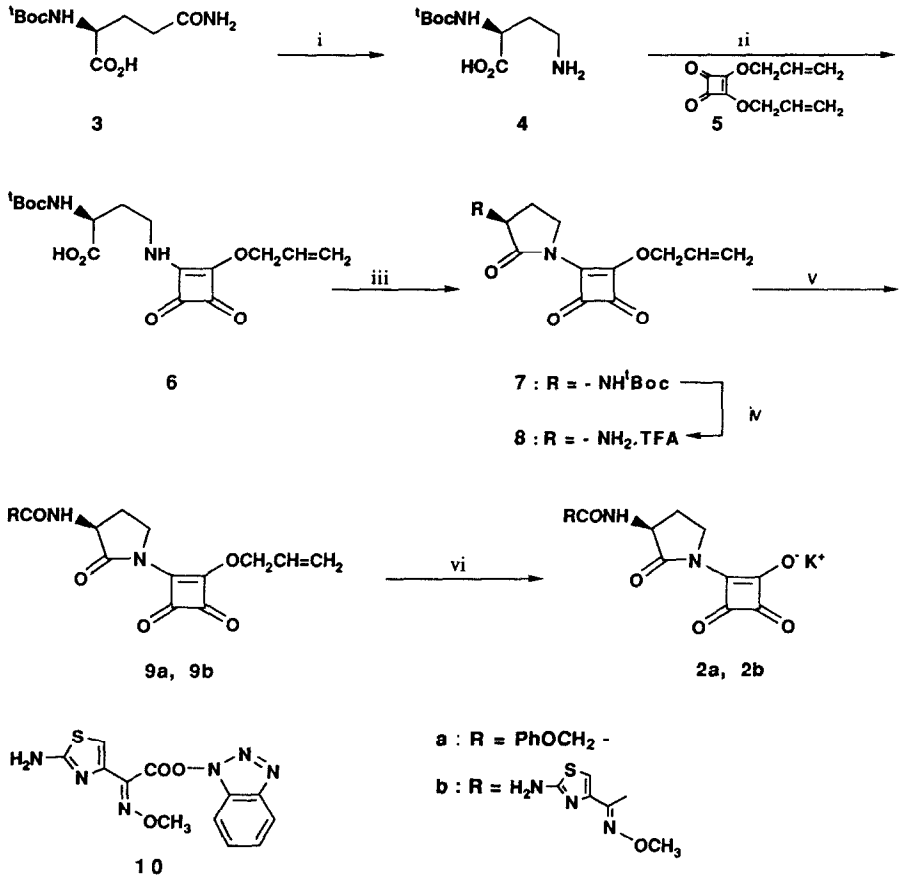
In the continuing search for new and novel lactam antibiotics, we recently reported[1] the synthesis of phenoxyacetyl-N-(hydroxydioxocyclobutenyl)-(L)-cycloserine (**1**), which was found to possess moderate antibacterial activity; however, it was also shown to have limited stability in aqueous solution. In recent years, a number of activated γ-lactam analogs of β- lactam antibiotics have been reported,[2] some of which have been found to exhibit various levels of antibacterial activity. It was therefore reasoned that γ- lactams **2**, activated by the electron withdrawing effects of the hydroxycyclobutenedione moiety and coupled with its acidic nature, would have the potential for useful antibacterial properties. Unlike the cycloserine derivative **1**, the lactams **2** were expected to be more stable chemically due to the lack of an electronegative oxygen attached directly to the lactam nitrogen. In this communication, we report the synthesis of hydroxycyclobutenedione-activated γ-lactams **2a** and **2b**.



1 : X = O, R = $PhOCH_2$ -
2a : X = CH_2 , R = $PhOCH_2$ -
2b : X = CH_2 , R = 

Since biologically active β-lactam and γ- lactam antibiotics possess an (S)-configuration at the carbon linked to the amide side chain, (L)-glutamine was chosen as the chiral precursor. N-^{t}Boc-(L)-glutamine (**3**) was converted to γ-aminobutyric acid **4**[3a] by a Hoffmann rearrangement of the amide using iodobenzene bis(trifluoroacetate).[3] Treatment of the crude product containing the γ- amino acid **4** with bisallyl squarate (**5**)[4] afforded γ-(allyloxydioxocyclobutenyl)aminobutyric acid **6**[5] in 67%

yield, based on **3**. The key step, an intramolecular acylation to the γ-lactam, was best achieved using dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide as the activating agents, producing N-(allyloxydioxocyclobutenyl)-γ-lactam **7**[5] in 73% yield. The amino-protecting group was removed by treatment with trifluoroacetic acid (TFA) and anisole to obtain α-amino-γ-lactam **8**[5] as a TFA salt which upon acylation with phenoxyacetyl chloride provided α-phenoxyacetamido-γ-lactam **9a**[5] in 20% yield. The allyl group was then cleaved catalytically using Pd(0) in the presence of potassium 2-ethylhexanoate[6] to afford the target γ-lactam **2a**[5] as a potassium salt in 59% yield, after purification on C-18 reverse phase silica. The corresponding aminothiazolylmethoxyiminoacetamido derivative



Reagents and Conditions:

i) $PhI(OCOCF_3)_2$/DMF-H_2O, pyr, rt; ii) Et_3N (1 eq)/THF, reflux, 7 hrs;
iii) DCC /N- hydroxysuccinimide(1 eq)/CH_2Cl_2, rt, 2 hrs; iv) TFA-anisole, 0-5° C, 10 min.;
v) For **9a**: $PhOCH_2COCl/Et_3N/CH_2Cl_2$, 0-5° C, 20 min.; For **9b**: **10**/CH_2Cl_2, rt, 2.5 hrs;
vi) $Pd(PPh_3)_4$/potassium 2-ethylhexanoate/EtOAc-CH_3CN, rt, 2 hrs.

2b[5] was obtained, albeit in low yield, by condensation of the amino lactam **8** with aminothiazolylmethoxyiminoacetic acid active ester **10**,[7] followed by removal of the allyl group.[6]

Hydrolytic stability of both γ-lactams **2a** and **2b** was examined in pH 7 buffer solution (conc. of **2**, ca. $5x10^{-4}$M) at room temperature (ca. 21°C). In contrast to the case for the cycloserine derivative **1**, no appreciable hydrolysis was detected for these γ-lactams after one week, indicating these γ-lactams were stable in aqueous solution. It was also found that these γ-lactams, **2a** and **2b** exhibited essentially no useful antibacterial properties against the microorganisms tested (e.g. *Staphyllococcus aureus, Streptococcus pneumoniae, Escherichia coli*).

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References and Notes

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2. a) For a recent review see J. E. Baldwin, G. P. Lynch and J. Pitlik *J. Antibiotics* **44**, 1 (1991).
   b) S.Coulton, I. Francois and R. Southgate *Tetrahedron Letters* **31**, 6923 (1990).

3. a) M. Waki, Y. Kitajima and N. Izumiya *Synthesis* 266 (1981).
   b) G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett and R. H. Boutin *J. Org. Chem.* **49**, 4272 (1984).

4. Prepared from squaric acid and allyl alcohol (U. S. Patent 4,092,146, May 30, 1978).

5. The ^{1}H-NMR of **6** indicated the presence of presumed geometrical isomer. All new compounds were characterized spectroscopically and by elemental analysis or by high resolution mass measurement. Selected physical data : Compound **6**: white foam ; $[\alpha]^{20}_D$ +2.04° (c 0.54, MeOH); IR (KBr): 3304(br), 2980, 1808, 1710, 1609 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.34 (9H, s), 1.74 (1H, m), 1.92 (1H, m), 3.34-3.57 (2H, m), 5.08 (2H, d, J = 5.4 Hz), 5.30 (1H, dd, J = 10.4, 5.8 Hz), 5.42 (1H, dd, J = 17.1, 10.4 Hz), 6.06 (1H, m), 6.94 (1H, d, J = 7.7 Hz, exchanged with D_2O), 8.66 (0.44H, br t, exchanged with D_2O), 8.86 (0.56H, br t, exchanged with D_2O); MS (Isobutane - DCI) m/e 355 (MH^+); HRMS (FAB/NOBA) Calcd for $C_{16}H_{22}N_2O_7$ (MH^+) 355.1505, found: 355.1509; UV (MeOH:H_2O, 1:1) λ max: 260 (ε = 1.91 x 10^4), 272 nm (ε = 1.92 x 10^4). Compound **7**: white crystals; mp 128-129°; $[\alpha]^{20}_D$ -43.63° (c 1.26, MeOH); IR(KBr): 2980,1808, 1755 (sh), 1740, 1712, 1596 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.37 (9H, s), 1.97-2.11 (1H, m), 2.28-2.38 (1H, m), 3.77 (1H, dt, J = 7, 10 Hz), 4.02 (1H, t, J = 10 Hz), 4.26 (1H, m), 5.21 (2H, d, J = 4.7 Hz), 5.33 (1H, d, J = 10.5 Hz), 5.46 (1H, d, J = 17.5 Hz), 5.98-6.11 (1H, m), 7.31 (1H, d, J = 8.5 Hz, exchanged with D_2O); ^{13}C NMR (75 MHz, DMSO-

d_6) δ ppm 25.78, 28.22, 42.69, 50.44, 73.68, 78.57, 119.55, 132.14, 155.24, 166.47, 171.79, 183.45, 186.33, 189.23; MS (methane - DCI) m/e 337 (MH^+), 309, 281; HRMS (FAB/NOBA) Calcd for $C_{16}H_{21}N_2O_6$ (MH^+) 337.1400, found: 337.1411; UV (MeOH:H_2O, 1:1) λ max: 254 (ε = 1.18 x 10^4), 294 nm (ε = 2.14 x 10^4); Anal. calcd for $C_{16}H_{20}N_2O_6.1/5H_2O$: C, 56.54; H, 6.05; N, 8.25. Found: C, 56.59; H, 5.96; N, 8.27. Compound **8**: white foam; $[\alpha]^{20}D$ -46.17° (C 1.19, MeOH); IR (KBr) : 3430, 1812, 1752, 1740 (sh),1678, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm : 2.04-2.18 (1H, m), 2.48-2.57 (1H, m), 3.83 (1H, dt, J = 6, 8, 10 Hz), 4.1 (1H, t, J = 9.5 Hz), 4.20 (1H, dd, J = 9, 10 Hz), 5.22 (2H, d, J = 5.3 Hz), 5.33 (1H, d, J = 10.5 Hz), 5.46 (1H, d, J = 17.2 Hz), 5.97-6.10 (1H, m), 8.67 (3H, br s, exchanged with D_2O); MS (FAB/NOBA) m/e 237 (as a free base+H); HRMS (FAB/NOBA) Calcd for $C_{11}H_{13}N_2O_4$ (MH^+) 237.0875, found: 237.0880; UV (MeOH:H_2O, 1:1) λ max: 250 (ε = 1.41 x 10^4), 298 (ε = 1.68 x 10^4); Compound **9a**: amorphous powder; $[\alpha]^{20}D$ -18.44° (c 0.24, MeOH); IR (KBr) : 1808, 1750 (sh), 1738, 1678, 1596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm : 2.15-2.23 (1H, m), 2.34-2.43 (1H, m), 3.86 (1H, dt, J = 7, 10 Hz) 4.09 (1H, t, J = 9 Hz), 4.66 (1H, m), 5.25 (2H, d, J = 5.4 Hz), 5.36 (1H, d, J = 10.4 Hz), 5.50 (1H, d, J = 17.2 Hz), 6.07 (1H, m), 6.97-7.01 (3H, m), 7.30-7.35 (2H, m), 8.63 (1H, d, J = 8.3 Hz, exchanged with D_2O); MS (FAB/NOBA) m/e 371 (MH^+); HRMS (FAB/NOBA) Calcd for $C_{19}H_{19}N_2O_6$ (MH^+) 371.1243, found: 371.1251; UV (MeOH:H_2O, 1:1) λ max: 254 (ε = 1.3 x 10^4), 294 nm (ε = 2.23 x 10^4); Anal. calcd for $C_{19}H_{18}N_2O_6.1/5\ H_2O$: C, 61.01; H, 4.97; N, 7.49. Found : C, 61.06; H,4.62; N, 7.08. Compound **2a**: white powder; $[\alpha]^{20}D$ -52.14° (c 0.28, MeOH); IR (KBr) : 3400, 1796, 1715 (sh), 1686, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm : 2.03 (1H, m), 2.3 (1H, m), 3.64 (1H, dt, J = 7,10 Hz); 4.02 (1H, t, J = 9 Hz), 4.49 (2H, ABq), 4.58 (1H, m), 6.92-6.97 (3H, m), 7.26-7.31 (2H, m), 8.48 (1H, d, J = 8.5 Hz); HRMS (FAB/NOBA) Calcd for $C_{16}H_{14}N_2O_6K$ (MH^+) 369.0489, found: 369.0497; UV (MeOH:H_2O, 1:1) λ max: 248 (ε = 1.45 x 10^4), 310 nm (ε = 1.63 x 10^4). Compound **2b**: white puffy solid; IR (KBr) : 3432 (br), 1798, 1716, 1584 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm : 1.95-2.05 (1H, m), 2.22-2.38 (1H, m), 3.49-3.65 (1H, m), 3.77 (3H, s), 4.01 (1H, t, J = 10 Hz), 4.55-4.61(1H, m), 7.05 (1H, s), 7.17 (2H, br s, exchanged with D_2O), 8.25 (1H, d, J = 8.5 Hz, exchanged with D_2O); MS (FAB/NOBA) m/e 380 (MH^+); HRMS (FAB/NOBA) Calcd for $C_{14}H_{14}N_5O_6S$ (MH^+) 380.0665; found: 380.0657; UV (MeOH:H_2O, 1:1) λ max: 202 (ε = 1.34 x 10^4), 246 (ε = 1.84 x 10^4), 308 nm (ε = 1.63 x 10^4).

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7. J. Blumbach, W. Durckheimer, J. Reden and H. Seliger (Hoechst A G), European Patent 0002774 (Sept. 23, 1981).