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SYNTHESIS OF α-(S)-ACYLAMINO-N-(HYDROXYDIOXOCYCLOBUTENYL)-β-LACTAMS AS POTENTIAL ANTIBIOTICS

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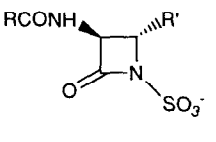
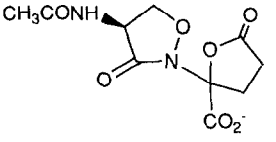
Abstract: Monocyclic β-lactams **6** activated by a hydroxycyclobutenedione moiety have been prepared as potential antibacterial agents from the natural amino acids, (L)-serine and (L)-threonine. These β-lactams were devoid of useful antibacterial activity.

The discovery of monocyclic lactam antibiotics, such as the monobactams[1] (**1**) and lactivicin[2] (**2**), resulted in intense research efforts directed towards the identification of unique antibacterial agents, such as general structures **3** and **4**, by the introduction of a variety of activating groups containing an anionic substituent (X = OSO_3^-, $OCH_2CO_2^-$, etc.) onto the monocyclic lactam skeleton.[3]



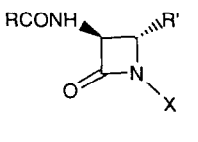
monobactams

1

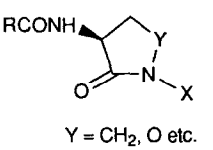


lactivicin

2



3

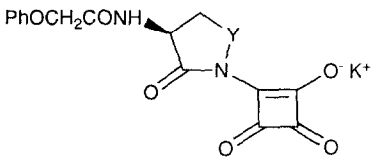


Y = CH_2, O etc.

4

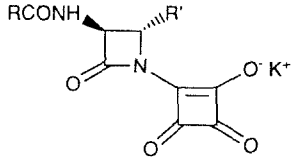
We recently reported the synthesis and antibacterial activity of α-acylamino-γ-lactams **5**, whose lactam amide is activated by the hydroxycyclobutenedione moiety.[4] Cycloserine derivative **5a** exhibited weak antibacterial activity and limited chemical stability in aqueous solution,[4a] whereas γ-lactam **5b** showed a lack of antibacterial activity and good stability in aqueous solution.[4b] In this paper, we describe the synthesis of α-acylamino-N-(hydroxydioxocyclobutenyl)-β-lactams **6**.

The hydroxycyclobutenedione unit in **6** is expected, by virtue of its electonegative effects, to activate the lactam amide via delocalization of the lone pair on the ring nitrogen, while simultaneously serving as the source of the anionic center. These two parameters are considered to be essential for the manifestation of useful antibacterial properties in β-lactam antibiotics.[3e,5]

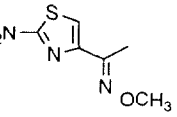


5a, Y = O

5b, Y = CH_2

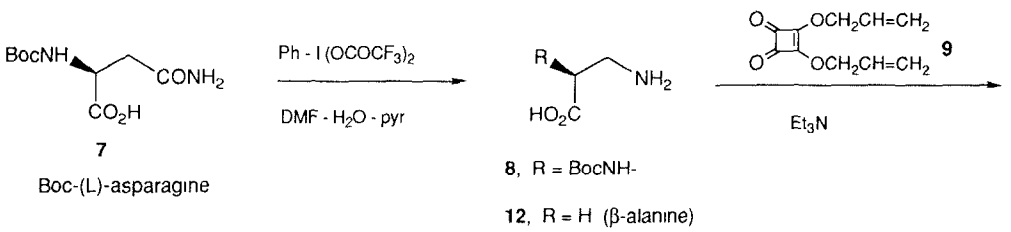


6a, R = $PhOCH_2$-, R' = H

6b, R =  R' = H

6c, R = $PhOCH_2$-, R' = CH_3

The synthetic approach, which was successfully applied to the preparation of γ-lactam **5b**,[4b] was considered initially for the construction of the β-lactam ring system. With the use of iodobenzene bis(trifluoroacetate),[6] N-Boc-(L)-asparagine (**7**) was converted to β-aminopropionic acid **8**, which was treated, without purification, with bisallyl squarate **9** to provide β-(allyloxydioxocyclobutenyl)aminopropionic acid **10**,[7] a potential synthetic intermediate for the β-lactam synthesis. Attempted intramolecular acylation of this cyclobutenylamino acid **10** to β-lactam **11** failed under the conditions (dicyclohexylcarbodiimide (DCC)/CH_2Cl_2) which were successful for the γ-lactam synthesis.[4b] Other conditions (e.g. DCC/N-hydroxysuccinimide/triethylamine, $(PhO)_2PON_3$, PPh_3/2-pyridyldisulfide, N-methyl-2-chloropyridinium iodide) were also attempted without success. Interestingly, the simple β-cyclobutenylaminopropionic acid **13**,[7] which was prepared from β-alanine **12** underwent cyclization, using DCC/N-hydroxysuccinimide/triethylamine[8] as activating agents, and furnished β-lactam **14**[7] in 24 % yield.

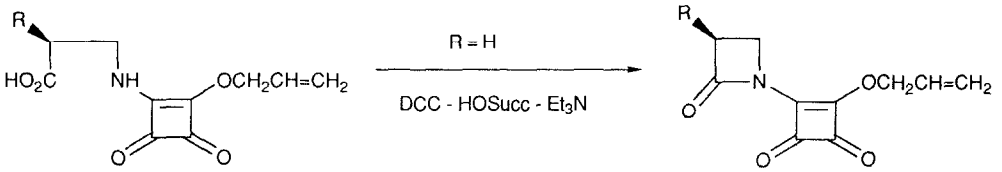


7

Boc-(L)-asparagine

8, R = BocNH-

12, R = H (β-alanine)



10, R = BocNH-

13, R = H

11, R = BocNH-

14, R = H

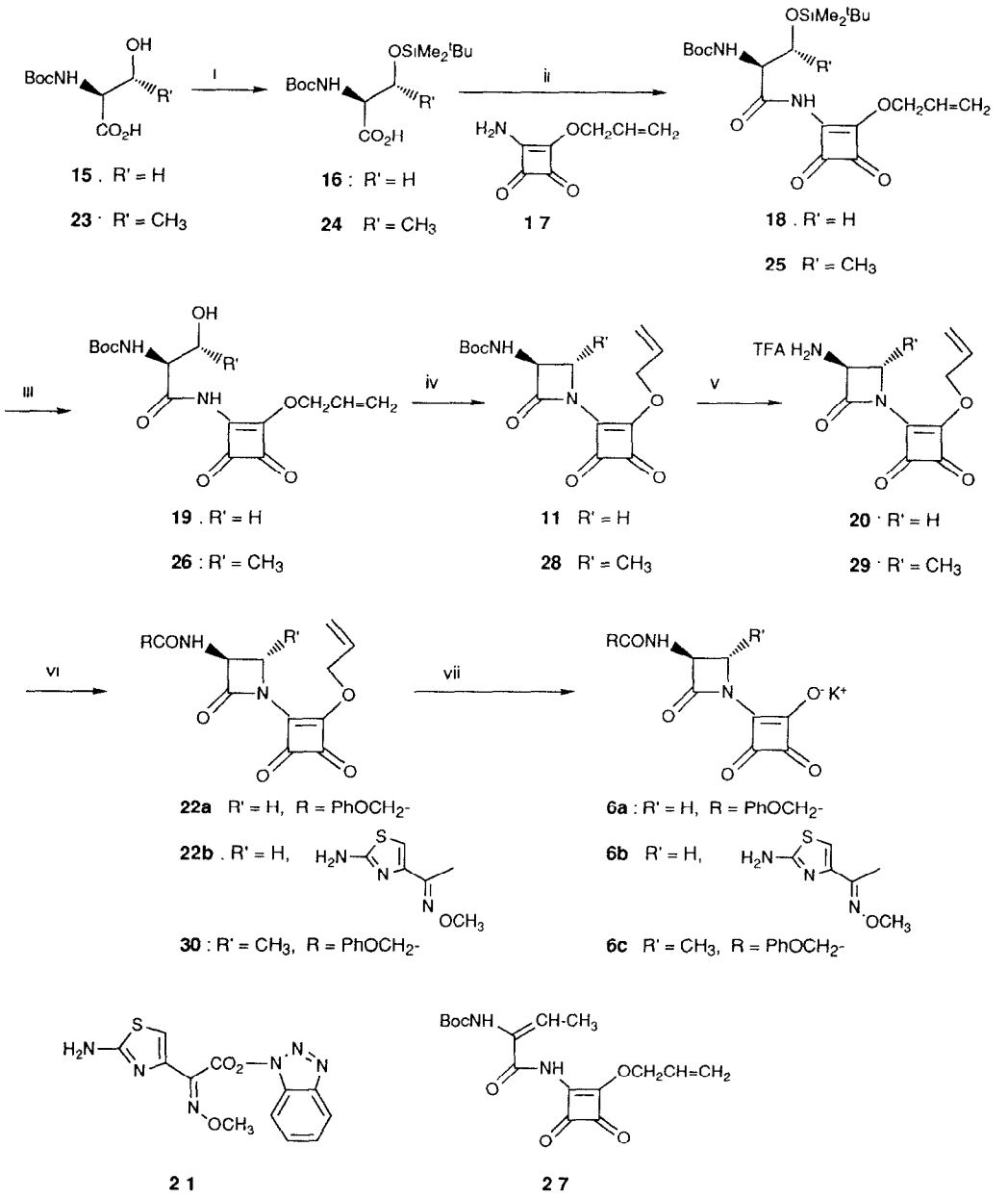
Because of the failure to generate α-Boc-amino-β-lactam **11** by an intramolecular acylation process, an alternative synthetic approach was investigated. Successful realization of α-Boc-amino-β-lactam **11** involved cyclization of the serine derivative **19** under Mitsunobu conditions,[9] a process which was originally developed for β-lactam construction by Miller and co-workers.[10]

Protection of N-Boc-(L)-serine (**15**) with t-butyldimethylsilyl chloride afforded the O-silylserine derivative **16**[7], which was condensed with aminoallyloxycyclobutenedione **17**[11] using the DCC/N-hydroxysuccinimide/triethylamine system, to furnish cyclobutenylamide **18**[7] in 36 % yield. Removal of the silyl protecting group with tetrabutylammonium fluoride produced the serine derivative **19**.[7,12] Because of the imide-like-NH of **19**, it was considered to be sufficiently acidic[13] for intramolecular alkylation to occur under Mitsunobu conditions.[10] Cyclization to the α-Boc-amino-β-lactam **11**,[7,14] indeed, proceeded smoothly with the use of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in THF. Removal of the Boc group in **11** was effected by treatment with trifluoroacetic acid (TFA) and anisole to provide α-amino-N-(cyclobutenyl)-β-lactam **20** as a TFA salt, which was in turn acylated with phenoxyacetyl chloride to give α-acylamino-β-lactam **22a**. The allyl group in **22a** was then cleaved using the $Pd(PPh_3)_4$-catalyzed deprotection reaction[15a] in the presence of N-methylaniline[15b] to afford the target β-lactam **6a**[7] as a potassium salt, after purification on C-18 reverse phase silica gel. The corresponding 3(S)-aminothiazolylmethoxyiminoacetamido-β-lactam **6b**[7] was prepared similarly from 3-amino-2-azetidinone **20** by acylation with aminothiazolylmethoxyiminoacetic acid active ester **21**[16] to **22b**, followed by cleavage of the allyl group. The aminothiazolylmethoxyiminoacetamido (ATMO) group was introduced as the C-3 substituent as this type of side chain is known generally to improve antibacterial activity in many β-lactam systems.[17]

Since the clinically proven monobactam antibiotic, aztreonam **1** (R= 2-aminothiazolyl-4-yl-methoxyimino-, R'=CH_3) possesses an α-methyl substituent at the 4-position of the azetidinone,[1] introduction of the α-methyl group into the 4-position of N-(hydroxydioxocyclobutenyl)-2-azetidinone was conducted with the expectation that it would improve the antibacterial properties of the system, particularly against Gram-negative organisms.

The approach used for the synthesis of **6a** was applied to Boc-(L)-threonine (**23**). The allyloxydioxocyclobutene derivative **26**[7] was prepared from Boc-(L)-threonine (**23**) in three steps via intermediates **24** and **25**.[7] In contrast to the serine series, cyclization of the threonine derivative **26** under Mitsunobu conditions (PPh_3 / DEAD) produced a noticeable amount of what appeared to be (H-NMR) the dehydro compound **27** along with the desired β-lactam **28**.[7] The target 4α-methyl analog **6c**[7] was obtained as a potassium salt from **28** by the same three step process (through **29** and **30**) described earlier for the serine series.

The cyclobutenedione-activated β-lactams **6** were found to be more labile than the γ-lactam **5b**[4b] but more stable than the cycloserine analog **5a**[4a] in pH 7 buffer solution, $T_{1/2}$[18] being about 3 days for **6a** and 7 days for **6c**. However, these monocyclic β-lactams **6** did not possess any useful antibacterial activity against a number of bacteria tested (e.g. *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*).



15 . R' = H
23 · R' = CH_3
16 : R' = H
24 R' = CH_3
17
18 . R' = H
25 R' = CH_3
19 . R' = H
26 : R' = CH_3
11 R' = H
28 R' = CH_3
20 · R' = H
29 · R' = CH_3
22a R' = H, R = $PhOCH_2$-
22b . R' = H,
30 : R' = CH_3, R = $PhOCH_2$-
6a : R' = H, R = $PhOCH_2$-
6b R' = H,
6c R' = CH_3, R = $PhOCH_2$-
21
27

Reagents and Conditions:

i) $^tBuMe_2SiCl$ / Im / DMF (**16**· y 59%, **24**. y.59%); ii) a) DCC / N-hydroxysuccinimide / CH_2Cl_2, b) **17** / Et_3N / CH_2Cl_2 (**18**. y 36%, **25**. y.12%); iii) TBAF-HOAc / THF (**19**· y.76%, **26**· y.71%); iv) PPh_3 / DIAD or DEAD / THF (**11**. y.35%, **28**. y 26%); v) TFA-anisole ; vi) $PhOCH_2COCl$ / Et_3N / CH_2Cl_2 for **22a** and **30** ; compound **21** / Et_3N / CH_2Cl_2 for **22b**, vii) a) $Pd(PPh_3)_4$ / CH_2Cl_2 / N-methylaniline, b) pH7 potassium phosphate buffer

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References and Notes

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7. All new compounds were characterized spectroscopically and by elemental analysis or by high resolution mass measurements. Selected physical data: Compound **11**: off-white solid; mp 105-107° C (CH_2Cl_2-Et_2O); $[\alpha]_D^{20}$ = +5.26° (c 0.095, EtOH); IR (KBr); 3360,1798, 1732, 1708 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_{ppm}: 1.43 (9H, s, ^tBu), 4.04 (1H, dd, J = 6.4 & 4.1 Hz, 4-H), 4.24 (1H, t, J = 6.6 Hz, 4-H), 5.07 (1H, m, 3-H), 5.28 (2H, d, J = 6.9 Hz, CH_2O), 5.38 (1H, dd, J = 10.4 & 1.2 Hz, $=CH_2$), 5.54 (1H, dd, J = 17.2 & 1.5 Hz, $=CH_2$), 6.13 (1H, m, CH=), 6.98 (1H, d, J = 7 Hz, NH, D_2O-exchanged); MS (isobutane-DCl) m/e 323 (MH+), 267; HRMS (FAB/ NOBA) calcd for $C_{15}H_{19}N_2O_6$ (MH^+) 323.1243, found 323.1239; UV (MeOH-H_2O = 1:1) λ_{max} 252 (ε 1.30 x 10^4), 296 nm (ε 1.80 x 10^4);Anal. Calcd for $C_{15}H_{18}N_2O_6$: C,55.90; H, 5.63; N, 8.69. Found: C, 56.07; H, 5.82; N,8.50. Compound **28**: gummy oil; $[\alpha]_D^{20}$ = +13.89° (c 0.54, MeOH); IR (film) 1820, 1790, 1740, 1714, 1600 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_{ppm}: 1.41 (9H, s, ^tBu), 1.66 (3H, d, J = 6.2 Hz, 4-Me), 4.44 (1H, m, 4-H), 4.52 (1H, dd, J = 7.8 & 3.5 Hz, 3-H), 5.29 (2H, d, J = 5.7 Hz, OCH_2), 5.37 (1H, d, J = 10.4 Hz, =CH), 5.54 (1H, d, J = 17.2 Hz, $=CH_2$), 6.12 (1H, m, CH=), 6.94 (1H, d, J = 7.2 Hz, NH); MS (FAB / Gly+NaCl) m/e 337

(MH+), 359 (MNa+). Compound **6a**: white puffy powder; IR (KBr) 3424, 1808, 1750, 1684, 1590, 1452 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 3.70 (1H, dd, J = 6 & 3.4 Hz, 4-H), 3.97 (1H, t, J = 6 Hz, 4-H), 4.53 (2H, s, OCH_2), 5.17 (1H, m, 3-H), 6.95-7.00 (3H, m, ArHs), 7.31 (2H, t, J = 8 Hz, *m*-ArHs), 8.93 (1H, d, J = 8.8 Hz, NH, D_2O-exchanged); MS (FAB/NOBA) m/e 335 (MH+). Compound **6b**: white puffy powder; IR (KBr) 3388 (br), 1808, 1766, 1670, 1568, 1446 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 3 93 (1H, dd, J = 6.3 & 3.2 Hz, 4-H), 4.05 (1H, t, J = 6.2 Hz, 4-H), 5.12 (1H, m, 3-H), 6.90 (1H, s, triazole-H), 9.38 (1H, d, J = 8.1 Hz, CONH); MS (FAB/NOBA) m/e 366 (M-K+2H+). Compound **6c**: white puffy powder; $[\alpha]_D^{20}$ = -51.11° (c 0.27, MeOH); IR (KBr) 3422, 1808, 1750, 1684, 1590 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6) δ_{ppm}: 1.50 (3H, d, J = 6.2 Hz, 4-Me), 4.1 (1H, m, 4-H), 4.53 (2H, s, OCH_2), 4.66 (1H, dd, J = 8.7 & 2.8 Hz, 3-H), 6.9-7.0 (3H, m, ArHs), 7.30 (2H, t, J = 7.8 Hz, ArHs), 8.91 (1H, d, J = 8.6 Hz, NH, D_2O-exchanged); MS (FAB/NOBA+KI) m/e 407 (MK^+); HRMS (FAB/NOBA) calcd for $C_{16}H_{14}N_2O_6K$ 369.0489, found 369.0490; UV (H_2O) λ_{max} 250 (ε 1.28 x 10^4), 312 nm (ε 1.48 x 10^4).

8. This condition was originally found to be successful for acylation of N-protected amino acid with aminoalkoxycyclobutenedione **17**.
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11. This compound was prepared from diallyloxycyclobutenedione **9** and ammonia in a mixture of Et_2O and n-petane. See Cohen, S.; Cohen, S.G. *J. Am. Chem. Soc.*, **1966**, *88*, 1533.
12. Purification of compound **19** was performed by column chromatography on silica gel using EtOAc-CH_2Cl_2 as a solvent system. Use of MeOH-CH_2Cl_2 as an eluent should be avoided since the serine derivative **19** was not stable on silica gel with this solvent system.
13. Apparent pKa of **19** in H_2O was measured as 6.17. For discussion on the acidity of the amide NH in β-lactam formation under Mitsunobu conditions, see a) Townsent, C.A.; Brown, A.M.; Nguyen, L.T. *J. Am. Chem. Soc.*, **1983**, *105*, 919, b) Miller, M.J.; Mattingly, P.G. *Tetrahedron* **1983**, *39*, 2563.
14. The β-lactam **11** decomposed rapidly on regular silica gel (E. Merck #7734). Purification of β-lactam **11** was achieved by column chromatogrphy on extra pure silica gel (E. Merck #7754) for characterization. The crude material was used for subsequent reaction.
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18. The time in which the half of the material was decomposed.