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SYNTHESIS OF A COGNITION ENHANCING BETA-LACTAM FUSED GAMMA-LACTAM

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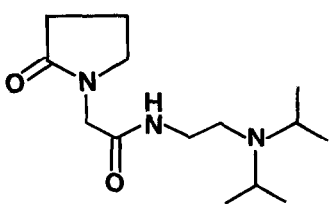
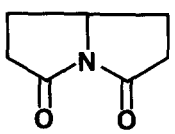
Abstract: The preparation and cognition enhancing properties of a highly strained beta-lactam fused gamma-lactam are reported.

Recent research to develop effective therapy for the treatment of Alzheimer's disease and associated cognitive disorders has focused on the synthesis of substituted pyrrolidinones such as pramiracetam[1] (1) and the novel bicyclic imides exemplified by CI-911[2] (rolziracetam, 2). To explore the relationship of ring size on cognitive efficacy we wished to synthesize the corresponding 4,5-fused analogue (3) which can be viewed as a beta-lactam fused pyrrolidinone.



1



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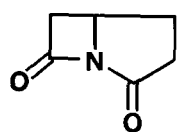
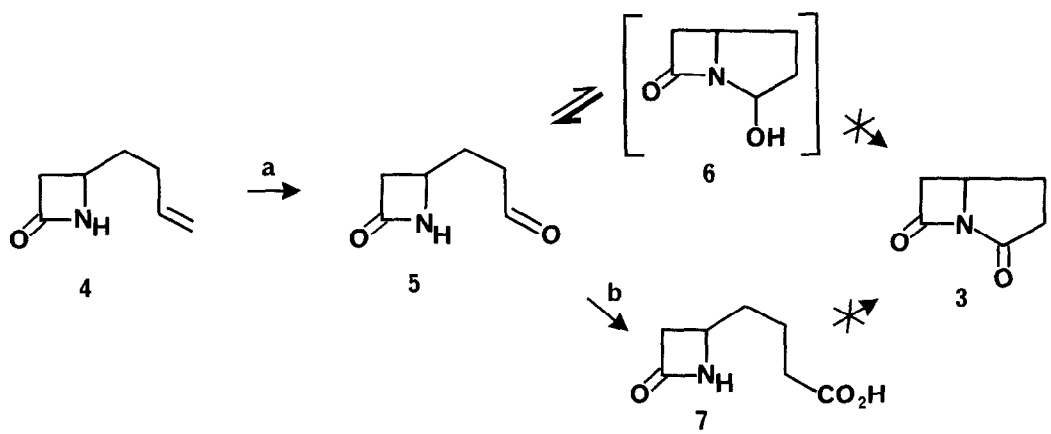


3

Two alternate but complimentary synthetic pathways were envisaged for the preparation of this strained bicycle and are shown in Schemes 1 and 2. Both routes used 4-(3-butenyl)-2-azetidinone[3](4) as a common starting

material but differed in the method by which the pyrrolidinyl ring would be generated. In the initial and most direct route (Scheme 1), 4-(3-butenyl)-2-azetidinone (4), prepared by the reaction of 1,5-hexadiene with chlorosulfonyl isocyanate, was ozonolyzed. Reductive workup gave the aldehyde (5) in 79% yield. The existance of the desired lactim (6) which would result from the closure of the azetidinone nitrogen on to the aldehydic carbonyl was not apparent from the NMR of this relatively unstable aldehyde. Limited attempts to generate such an intermediate and subsequently oxidize it to the desired beta-lactam fused azetidinone were not encouraging and it was decided to pursue an alternate route to (3) through a dehydrative cyclization of the 4-oxo-2-azetidinebutanoic acid (7).

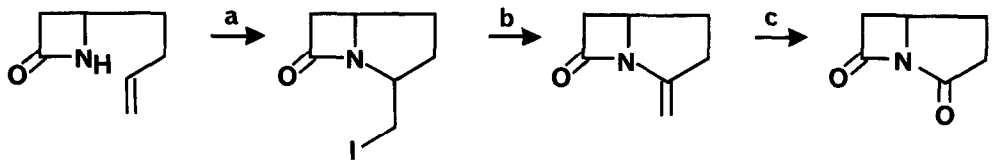
Scheme 1



a = O_3, CH_2Cl_2/MeOH, -78°C, followed by $(CH_3)_2S$, -78°C - RT;
b = 1.5eq MCPBA/CH_2CL_2/RT

Ozonolysis of (4) followed by oxidative workup with meta-chloroperbenzoic acid (MCPBA) gave the desired acid (7). The poor reproducibility of this reaction caused us to investigate an alternate procedure in which the aldehyde could be oxidized directly to (7). Treatment of the aldehyde (5) with meta chloroperbenzoic acid[5] followed by concentration and trituration with ether gave (7) as a pure solid (59%). Despite ample precedent from the synthesis of CI-911 and its derivatives, 4-oxo-2-azetidinebutanoic acid (7) could not be cyclized to the target imide under dehydrating conditions.

Scheme 2



4 8 9 3

a = I_2, propylene oxide/CH_2Cl_2, RT; b = DBU/THF, RT; c = O_3/CH_2Cl_2/MeOH, -78°C, followed by $(CH_3)_2S$, -78°C - RT

The second and ultimately successful route to the preparation of (3), Scheme 2, proceeded through the known 2-(iodomethyl)-1-azabicyclo[3.2.0]-heptane-7-one[3] (8). In our hands, the preparation of (8) through the cyclization of (4) with iodine and sodium bicarbonate[6] gave (8) as an oil in variable and poor yield. Changing the acid scavenger to propylene oxide afforded (8) as a crystalline (mp 37-37.5°C[7]) and sublimable solid in modest but reliable yield (45%). This improvement may result from the homogeneous rather than the heterogeneous nature of the acid scavenger. Elimination of iodide proceeded cleanly using 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as base to give the exomethylene substituted fused beta lactam[8] (9) in 75% yield (ir ($CDCl_3$) 1763 cm^{-1}, mp 30-31°C[7]). This was isolated as a colorless crystalline solid by chromatography and vacuum sublimation. Ozonolysis of (9) with reductive workup gave the target beta lactam fused pyrrolidinone (3) as an analytically pure solid[9] (mp 61-63°C, 50%). This highly strained structure (ir (KBr) 1845, 1810, 1720 cm^{-1}) was found to exhibit surprising stability[10] both in solution, upon chromatography and as a solid, which underwent no observable decomposition when stored for extended periods at -15°C.

Pharmacological evaluation in an amnesia reversal based cognitive paradigm revealed that (3) possessed significant cognitive enhancing properties which were, however, inferior to those of its homolog CI-911. Evaluation of its antibacterial spectrum showed this novel strained beta lactam to be devoid of significant activity.

References

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4. The addition of methanol as cosolvent significantly improved the isolated yield of aldehyde from ozonolysis.

5. G. Zweifel and H. Arzoumanian, J. Amer. Chem. Soc., **1967**, 89, 291.

6. An attempted alternate cyclization mediated by phenylselenenyl bromide gave direct addition of the phenylselenenyl group to the azetidinone nitrogen. Oxidative workup reafforded the starting azetidinone. A related observation has been reported recently; A. Toshimitsu, K. Tereo and S. Uemura, J. Org. Chem., **1986**, 51, 1724.

7. Recrystallized from heptane.

8. Of particular note in the complex NMR of (9) was significant long range coupling between the C_5 bridging proton and the exomethylene group.

9. This compound could also be sublimed.

10. The moderate stability of a closely related structure has also been noted, R.W. Ratcliffe, T.N. Salzman and B.G. Christenson, Tet. Lett., **1980**, 21, 31.

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