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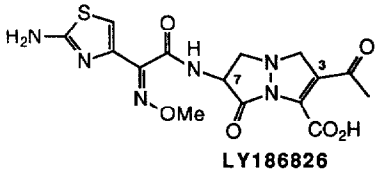
BICYCLIC PYRAZOLIDINONE ANTIBACTERIAL AGENTS. SYNTHESIS OF SIDE CHAIN ANALOGUES OF CARBAPENEMS PS-5 AND THIENAMYCIN

Louis N. Jungheim
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, IN 46285

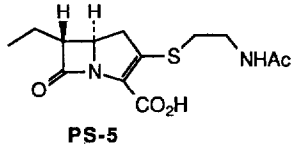
Abstract: Bicyclic pyrazolidinone analogues of carbapenems, bearing either an ethyl or hydroxyethyl side chain at C-7, were prepared via the 1,3-dipolar cycloaddition chemistry of pyrazolidinium ylides.

Recently we described a new class of synthetic γ-lactam antibacterial agents, the bicyclic pyrazolidinones, represented by LY186826.[1] These novel compounds exhibit broad spectrum antibacterial activity against a variety of clinically important pathogens. The mechanism of action of the bicyclic pyrazolidinones is the same as that of β-lactam antibiotics: they inhibit the penicillin binding proteins involved in bacterial cell wall biosynthesis.[2]

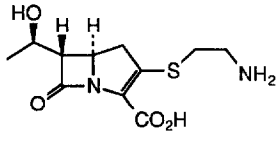
Our initial work in this area revolved around compounds bearing typical cephalosporin acylamino side chains at C-7. As with cephalosporins, modification of the C-7 side chain has a dramatic effect on the antimicrobial spectrum and potency of bicyclic pyrazolidinones.[3] Carbapenems, represented by PS-5 and thienamycin, are potent naturally occuring β-lactam antibiotics which possess an alkyl or substitued alkyl moiety instead of the acylamino side chain common to cephalosporins and penicillins. Herein, we report on the synthesis of bicyclic pyrazolidinones with carbapenem type side chains at C-7.



LY186826



PS-5

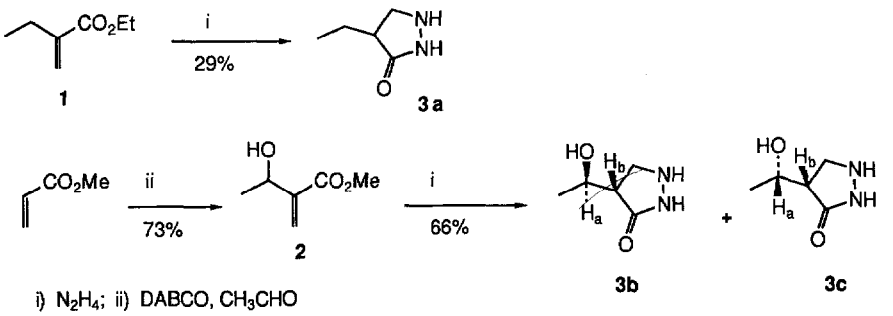


Thienamycin

The requisite pyrazolidinone starting materials were prepared in straightforward fashion by condensing anhydrous hydrazine with substituted acrylates 1 or 2 (Scheme 1). The hydroxyethyl substituted pyrazolidinones 3b,c were obtained as a 1:1 mixture of diastereomers which were

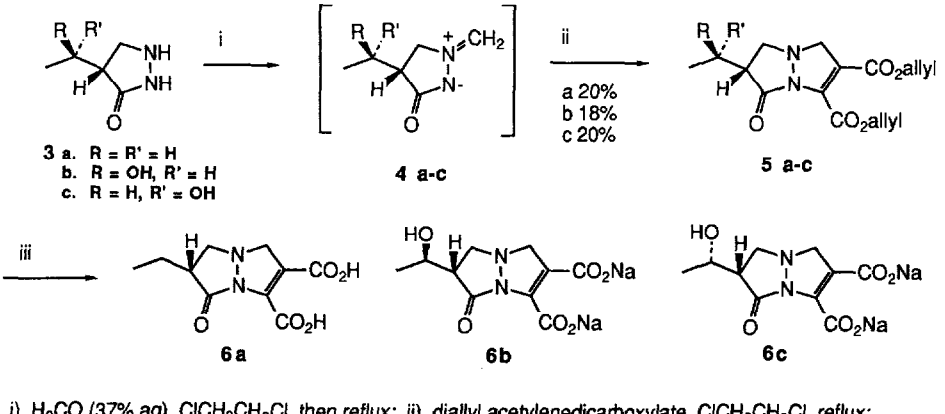
readily separated by flash chromatography (15% MeOH/CH_2Cl_2).[4] Stereochemical assignments were made based upon proton NMR coupling constants: J_{ab}=2.5Hz for 3b and J_{ab}=7.5Hz for 3c.[5] The more polar isomer 3b possesses the thienamycin relative stereochemistry, albiet in racemic form.

Scheme I



Pyrazolidinones 3a-c were converted to the desired bicyclic series via the 1,3-dipolar cycloaddition chemistry of the corresponding pyrazolidinium ylides 4a-c [1] (Scheme II). The ylides are generated in situ by treating 3a-c with aqueous formaldehyde followed by heating to reflux in 1,2-dichloroethane. Diallyl acetylenedicarboxylate readily underwent cycloaddition with these ylides giving rise to 5a-c. Removal of the allyl esters via the method of McCombie[6] completed the preparation of C-3 carboxy-substituted bicyclic pyrazolidinones 6a-c.

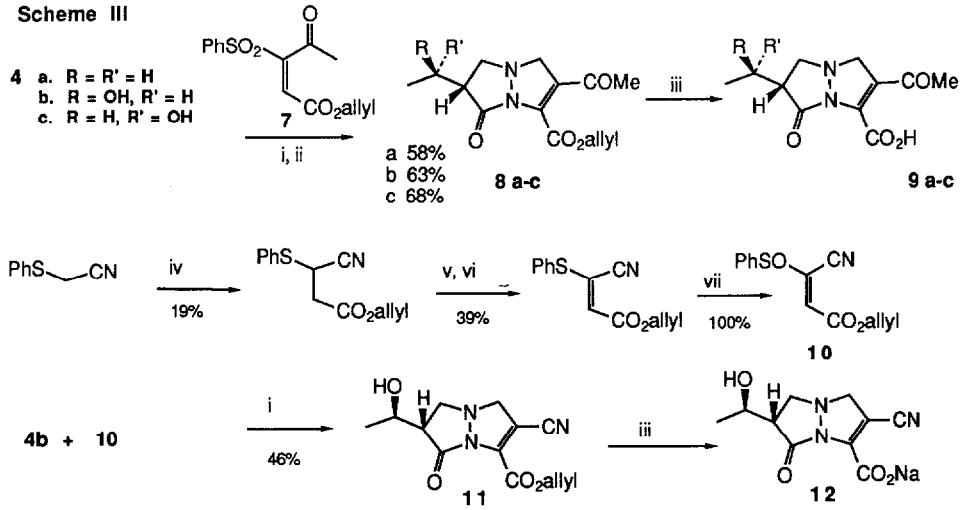
Scheme II



Next, we sought to prepare the C-3 keto-substituted analogues 9a-c for comparison to LY186826. When unsymmetrical acetylenes are employed in the 1,3- dipolar cycloaddition approach mixtures of regioisomers are often obtained.[1] We have reported the use of vinyl sulfones as acetylene equivalents to provide bicyclic pyrazolidinones in a highly regioselective fashion.[7] The

(E)-olefin geometry is required for high regioselectivity to be obtained. Ylides 4a-c underwent 1,3-dipolar cycloaddition with vinyl sulfone 7[7] and subsequent base catalyzed elimination of benzenesulfinic acid to give 8a-c. In each instance, less than 5% of the undesired regioisomer was observed by NMR. Pd(0) mediated allyl ester deprotection gave rise to the desired acids 9a-c.

Scheme III



i) $ClCH_2CH_2Cl$,reflux; ii) N-methylmorpholine; iii) $Pd(OAc)_2$, Ph_3P, sodium-2-ethylhexanoate, acetone
iv) $BrCH_2CO_2R$, $LiN(TMS)_2$, 0°; v) NCS, CCl_4, THF, reflux;
vi) DBU, CH_2Cl_2, -78°, separate isomers; vii) m-CPBA, CH_2Cl_2, -78°

Electron withdrawing substituents at C-3 of the bicyclic pyrazolidinone nucleus have a beneficial effect on the antimicrobial spectrum and potency, e.g. the C-3 cyano-substituted analogue of LY186826 is considerably more potent than LY186826 itself.[8] Nitrile 12 was prepared via cycloaddition of the (E)-vinyl sulfoxide 10[9] followed by *in situ* thermal elimination of benzene sulfenic acid to give 11 (Scheme III). Palladium catalyzed deblocking completed the synthesis of 12. Compounds 6a-c, 9a-c and 12 were tested for antibacterial activity. While 12 was the most potent compound in this series, all of the C-7 alkyl-substituted bicyclic pyrazolidinones exhibited significantly reduced antibacterial activity relative to LY186826.[10]

REFERENCES AND NOTES

1. Jungheim, L. N.; Sigmund, S. K. J. Org. Chem. 1987, 52, 4007 and references therein.
2. Allen, N. E.; Hobbs, J. N. Jr.; Wu, E. in Antibiotic Inhibition of Bacterial Cell Surface Assembly and Function; Actor, P.; Daneo-Moore, L.; Higgins, M. L.; Satton, M. R. J.; Shockman, G. D., Eds.; American Society for Microbiology, Washington D. C., 1988; p 569.
3. Jungheim, L. N.; Barnett, C. J.; Shepherd, T. A. "Bicyclic Pyrazolidinones. Side Chain SAR of Antibacterial Agent LY186826." Medicinal Chemistry Abstract #68, Third Chemical Congress of North America, Toronto, Canada, 1988.
4. Satisfactory spectral data were obtained for all new compounds. Representative NMR spectral data: 3b (90MHz, $CDCl_3$): δ 5.2 (bs, 2); 4.32 (dq, 1, J=2.5, 6.5); 3.7-3.4 (m, 2); 3.48 (s, 1); 2.56 (dm, 1, J=2.5); 1.24 (d, 3, J=6.5). 3c (90MHz, $CDCl_3$): 8.0 (bs, 1); 4.4 (bs, 1); 3.92 (dq, 1, J=7.5, 6.5); 3.54 (dd, 1, J=8, 11); 3.42 (s, 1); 3.15 (t, 1, J=11); 2.60 (m, 1); 1.20 (d, 3, J=6.5). 9b (300 MHz, D_2O):4.35 (dm, 1, J=3); 4.2 (d, 1, J=12); 3.95 (d, 1, J=12); 3.7 (m, 1); 3.25 (m, 2); 2.35 (s, 3); 1.25 (d, 3, J=7). 9c (300 MHz, D_2O):4.20 (quintet, 1, J=7); 4.15 (d, 1, J=12); 3.95 (d, 1, J=12); 3.64 (m, 1); 3.28 (m, 2); 2.35 (s, 3); 1.30 (d, 3, J=7). 12 (300 MHz, D_2O): 4.32 (dq, 1, J=3.5, 7.5); 4.22 (d, 1, J=11.5); 4.04 (d, 1, J=11.5); 3.72 (t, 1, J=9); 3.37 (t, 1, J=9); 3.25 (dm, 1, J=3.5); 1.28 (d, 3, J=7.5).
5. Aldol condensation products exhibt J_{ab} (erythro)<J_{ab} (threo). Evans, D. A.; Nelson, J. V.; Vogel, E. J. Am. Chem. Soc. 1981, 103, 3099.
6. Jeffrey, P. D.; McCombie, S. W. J. Org. Chem. 1982, 47 587.
7. Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepherd, T. A.; Sigmund, S. K. Tetrahedron. 1988, 44, 3119.
8. Ternansky, R. J.; Draheim, S. E.; Pike, A. J.; Ott, J. L. "Pyrazolidinone Antimicrobial Agents. Synthesis and In Vitro Activity of New Highly Potent Analogues." Abstract #1213, XXVII Interscience Conference on Antimicrobial Agents and Chemotherapy, 1987.
9. Prepared following the method of: Boyd, D. B.; Foster, B. J.; Hatfield, L. D.; Hornback, W. J.; Jones, N. D.; Munroe, J. E. and Swartzendruber, J. K. Tetrahedron Lett. 1986, 27, 3457. A significant amount of phenylthioacetonitrile was recovered from the alkylation reaction under a variety of reaction conditions. The starting material was separated from the alkylation product on a Waters Prep 500 system (toluene - 1% EtOAc/toluene gradient). The subsequent chlorination-elimination steps gave a mixture of (E)- and (Z)-olefin isomers which were separated by flash chromatography (1% EtOAc in toluene).

10. We are grateful to Jack Westhead and Ernie Wu for the biological evaluation of these compounds.

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