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ADDITION OF PENICILLIN GRIGNARDS TO GLYOXALS A SYNTHESIS OF NOVEL PENAM KETOALCOHOLS[1]

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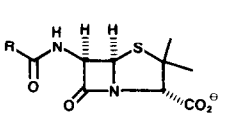
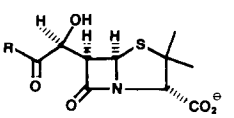
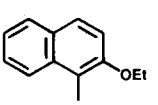
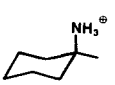
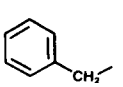
Summary: The condensation of penicillin Grignards with substituted glyoxals leads to the synthesis of novel penam α-ketoalcohol antibacterials which are structurally related to several clinically useful penicillins.

Over the last forty years, an enormous effort has been focused on the discovery of β-lactam antibiotics.[2] While many of the structural prerequisites for the antibacterial activity of β-lactams are now well defined, the precise role of the amide/alcohol side chains is not. Amide side chain substitution determines in large part the antibacterial spectrum, β-lactamase stability and pharmacologic properties of penicillins. In this communication, we shed additional light on the structural/conformational side chain features that are responsible for the biological profile of penicillins with the synthesis of novel penam α-ketoalcohols **1-3** which are possible amide surrogates[3] of several clinically useful penicillins.





	R	
Nafcillin		1
Cyclacillin		2
Penicillin G		3

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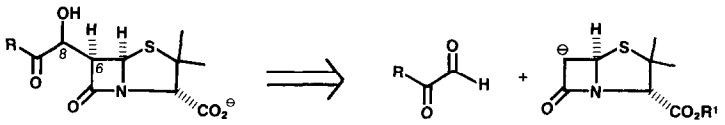
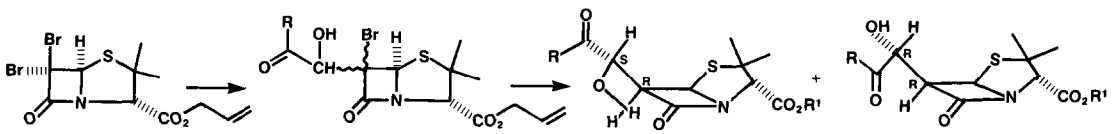
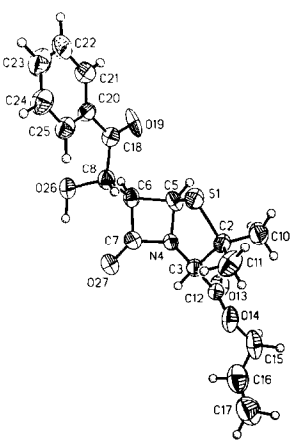


A synthesis of the desired α-ketoalcohols suggested a condensation between C-6 penicillin carbanions and glyoxals.[4] In practice, however, these unsubstituted anions[5] lack the stability and stereospecificity required for this aldol condensation. Therefore, the dibromopenicillanic ester route (shown below), which establishes the requisite 6R stereochemistry was employed. Treatment of penicillin Grignard derived from **4**[6] in toluene at -78°C with freshly distilled phenyl glyoxal[7] provided a mixture of three isomeric bromides[8] which were best not isolated but directly subjected to tributyltin hydride reduction[9] to afford after silica gel chromatography a mixture of ketoalcohols **6a** and **7a** (R = phenyl; R^1 = allyl)[10] in ca. a 3:1 ratio.



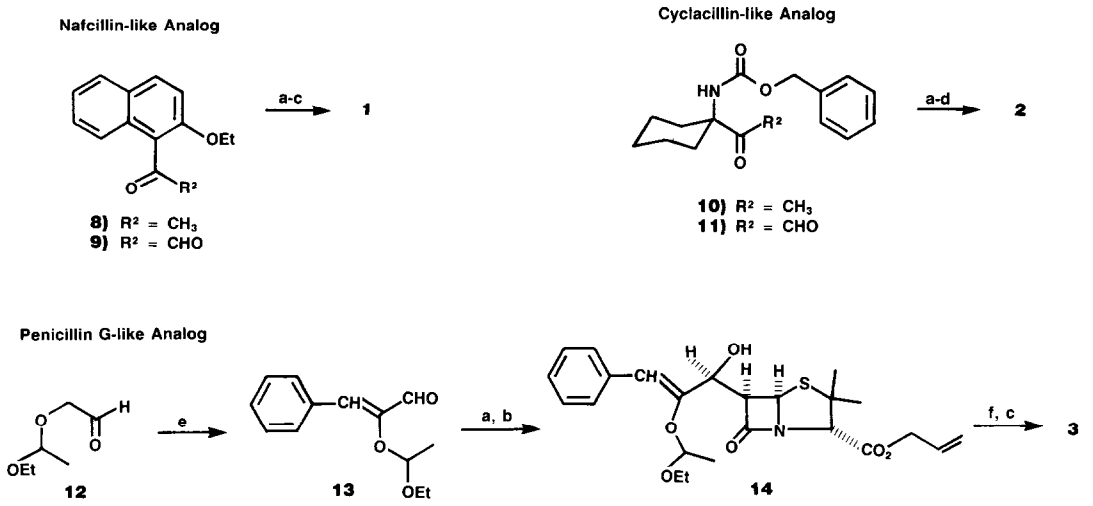
4 **5** **6** **7**

The 8S stereochemistry of the major product **6a** (R = phenyl; R^1 = allyl) was predicted by model studies[11] with acetaldehyde and confirmed by single crystal x-ray analysis.[12] Proton NMR (H_2O) of the potassium salt of each isomer suggests in solution a near periplanar orientation of H-6 and H-8 (**6b**: $J_{6,8}$ = 9.88 Hz; **7b**: $J_{6,8}$ = 9.52 Hz).[13] Both isomeric salts have good solution stability (T½ in pH 7 phosphate buffer >3 days). The 8S isomer **6b** (R = phenyl, R^1 = potassium) has superior antibacterial activity (Table 1) and may well possess a ground state conformation that mimics the penicillin side chain by virtue of a hydroxyl hydrogen bond to the β-lactam carbonyl.



6a

Selenium dioxide treatment of ketone **8**[14] (2 equiv SeO_2/dioxane-H_2O/24 hrs) afforded glyoxal **9** which was subjected to the abovementioned methodology to yield, after a palladium mediated transesterification,[15] penam **1**[10] (nafcillin analog). Similarly, ketone **10** generated from 1-amino-1, 1-pentamethylene-2-propanone hydrochloride[16] was oxidized to glyoxal **11** and converted to cyclacillin-like penam **2**.[10]



a) 1 equiv **4**, toluene or CH_2Cl_2, -78°, 1 equiv CH_3MgBr, 1 equiv aldehyde (toluene or CH_2Cl_2), 2 hrs, NH_4Cl. b) 1-2 equiv n-Bu_3SnH, AIBN, toluene, 80°, 3-5 hrs, silica gel chromatography, 30-40% from aldehyde. c) $(\varnothing_3P)_4$ Pd, $\varnothing_3P$, 1 equiv potassium 2-ethyl hexanoate, ~80%. d) H_2/Pd/celite MeOH/H_2O, ~80%. e) 5% NaOH/MeOH/benzaldehyde, 48%. f) 0.1N HCl/THF, 1 hr, 98%.

A masked glyoxal was required for the synthesis of penam **3** analogous to penicillin G. Aldehyde **12** was condensed with benzaldehyde to afford α,β-unsaturated aldehyde **13**[10] which was converted to alcohol **14**.[10] Acid hydrolysis followed by removal of the allyl ester moiety yielded penam **3**.[10]

Table 1
IN VITRO **ANTIBACTERIAL ACTIVITY (μg/ml)**

Organism		*Nafcillin*	*1*	*Cyclacillin*	*2*	*Penicillin G*	*3*	*6b*	*7b*
Staphylococcus aureus	01A005	0.39	50	0.78	200	0.05	6.25	3.12	50
Staphylococcus aureus	01A400	0.20	50	12.5	200	25	12.5	6.25	100
Streptococcus pyogenes	02C054	<0.025	6.25	0.10	200	0.025	0.39	<0.39	12.5
Neisseria sicca	66C000	12.5	100	0.78	200	0.05	3.12	3.12	50

A portion of the antibacterial activity of the described α-ketoalcohols is shown in Table 1. Nafcillin and cyclacillin amide surrogates **1** and **2** suffered a substantial loss in activity. On the other hand, penicillin-G-like analog **3** retained significant antibacterial activity, most notably against β-lactamase producing *Staphylococci* (01A400). The 8S α-ketoalcohols are, in addition, potent β-lactamase inhibitors (Table 2). A more extensive profile of these and other analogs will be reported.

Table 2
CELL FREE β-LACTAMASE INHIBITION

Source of β-*Lactamase*		*[I] μm/[s] μm*	*% Inhibition of Substrate Hydrolysis*[17]					
			1	*2*	*3*	*6*	*7*	*Clavulanic Acid*
Staphylococcus aureus	01A400	8/32	20	70	97	99	64	85
Escherichia coli	51A129	1/32	70	74	91	94	14	81

[I] inhibitor concentration; [s] ampicillin concentration

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References and Notes

1) We (DAC and RAV) dedicate this paper to the memory of a friend and colleague (LAR) who provided the inspiration for this work.

2) 'Cephalosporins and Penicillins — Chemistry and Biology,' ed. E.H. Flynn, Academic Press, New York, 1972, R.W. Ratcliffe, G. Albers-Schonberg in "Chemistry and Biology of β-Lactam Antibiotics." R.B. Morin and M. Gorman Eds. Academic Press, New York, 1982, T. Kametani, *Heterocycles* **17** 463 (1982). M. Shibuya, J. Synth, *Org. Chem. JPN* **41** 62 (1983). R. Labia and C. Morin, *J. Antibiotics* **37** 1103 (1984).

3) J.S. Morley, *Trends Pharmacol. Sci.* **1** 463 (1980).

4) While Grignard/glyoxylate condensations have been explored in depth (see "Asymmetric Organic Reactions" J.D. Morrison and H.S. Mosher, Prentice Hall Inc. 50 (1976)), to the best of our knowledge, Grignard addition to substituted glyoxals has not been examined.

5) F. DiNinno, T.R. Beattie and B.G. Christensen, *J. Org. Chem.* **42** 2960 (1977).

6) R.A. Volkmann, R.D. Carroll, R.B. Drolet, M.L. Elliott and B.S. Moore, *J. Org. Chem.* **47** 3344 (1982).

7) Free aldehyde must be generated prior to the Grignard addition and in most cases is best obtained by thermal "cracking' (distillation) or azeotropic removal of water from the hydrate. For the preparation of glyoxals see: R.B. Moffett, B.D. Tiffany, B.D. Aspergren and R.V. Heinzelman, *J. Amer. Chem. Soc.* **79** 1687 (1957). K. Schank, *Chem. Ber.* **100** 2292 (1967). H.D. Becker, G.J. Mikol and G.A. Russell, *J. Amer. Chem. Soc.* **85** 3410 (1963).

8) Based on previous work, we believe 5 to consist of the (6S,8S), (6R,8S) and the (6R,8R) isomers. The ratio of products is solvent dependent. More of the desired 8S products are produced in toluene or CH_2Cl_2 (see Ref. 11).

9) J.A. Aimetti, E.S. Hamanaka, D.A. Johnson and M.S. Kellogg, *Tetrahedron Letters* 4631 (1979).

10) Satisfactory spectral and analytical data was obtained for this compound. None of the reported yields have been optimized.

11) B.B. Brown and R.A. Volkmann, *Tetrahedron Letters* 1545 (1986).

12) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

13) The 'H NMR and x-ray analysis suggest a similar (solution/crystal) side chain conformation of **6**. The side chain conformation of **7** is at this juncture speculative.

14) M.P. Gupta and M. Sahu, *Z. Kristallogr., Kristallgeom, Kristallphys. Kristallchem.*, **135** 262 (1972). R.B. Girdler, P.H. Gore and J.A. Hoskins, *J. Chem. Soc.* (C) 181 (1966).

15) P.D. Jeffrey and S.W. McCombie, *J. Org. Chem.* **47** 587 (1982).

16) M. Samiev, E.F. Venger, E.M. Glazunova and V.I. Nikitin, *Dokl. Akad. Nauk Tadzh. SSR* **15** 33 (1972). C.L. Klein, R.J. Majeste, A.E. Luedtke, W.J. Ray, E.D. Stevens and J.W. Timberlake, *J. Org. Chem.* **49** 1208 (1984).

17) Modified Novick assay measuring cell free β-lactamase inhibition by examining the ability of the compound to inhibit the β-lactamase mediated hydrolysis of ampicillin (10 min incubation). See J.A. Retsema, A.R. English and A.E. Girard, *Antimicrob. Agents Chemother.* **17** 615 (1980).

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