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3-(1'-HYDROXYETHYL)-2-AZETIDINONES FROM 3-HYDROXYBUTYRATES AND N-ARYLALDIMINES

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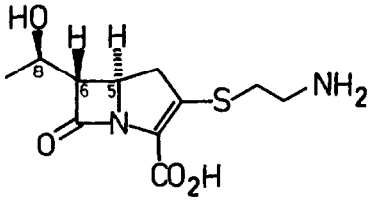
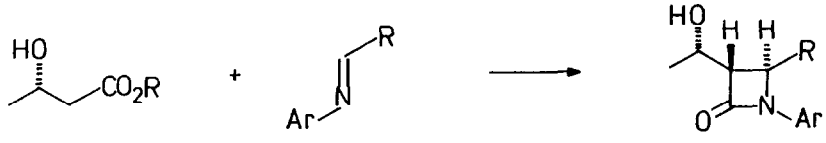
Abstract:
Dianion imine addition, cyclisation reaction between ethyl-3-hydroxybutyrate and aldimines generates β-lactams with the hydroxyethyl sidechain of thienamycin and related β-lactam antibiotics in place. The effects of the N-arylaldimine and the reaction conditions on the sterochemistry of the resulting products are examined.

The outstanding biological properties of thienamycin and related β-lactam antibiotics as well as their unique structure consisting of a highly strained bicyclic ring system concomitant with three chiral centres has prompted enormous synthetic efforts towards their total synthesis.[2,3]



Thienamycin

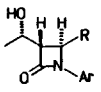
We and others have recently demonstrated[4] the feasibility of adding the dianion of 3-hydroxybutyrates to aldimines,[5] thus generating β-lactams with the hydroxyethyl sidechain of thienamycin and related carbapenems in place in a one flask procedure (1).

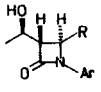


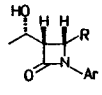
(1)

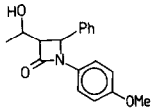
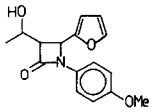
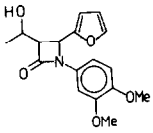
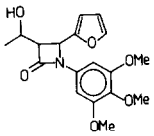
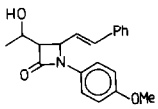
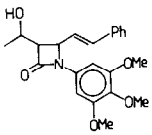
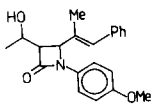
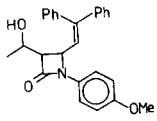
The use of esters of 3-hydroxybutyrates as chiral building blocks is of particular advantage because they are readily available in both enantiomeric forms[6] and can be α-alkylated in a highly diastereoselective manner.[7] The great interest in this novel reaction has caused us now to report some of our preliminary findings.

Table 1: 3-(1'-Hydroxyethyl)-2-Azetidinones


a


b


c

	β-Lactam	Run	Procedure	Yield (%)	Ratios (%) a	b	c
1		1	A	45	95	5	--
		2	B	42	60	--	40
2		3	A	59	50	50	--
		4	B	50	20	--	80
3		5	A	59	50	50	--
		6	D	46	65	20	15
4		7	A	29	80	20	--
5		8	A	59	95	5	--
6		9	A	77	50	25	25
		10	B	67	50	10	40
		11	C	77	50	10	40
		12	D	77-98	50	--	50
		13	E	66	50	--	50
7		14	A	20	70		30
8		15	A	35	70		30
9		16	A	77	70		30

Procedures[8]: A: THF/HMPA; rt. B: THF/HMPA; -20°C. C: THF/HMPA; +10°C.
D: THF; +10°C; E: THF, -20°C.

A series of 3-(1'hydroxyethyl)-2-azetidinones (Table I) was synthesized via this novel addition cyclisation reaction from racemic ethyl-3-hydroxybutyrate and nonenolizable N-arylaldimies. We studied the effects of the imine substituents as well as the effect of various reaction conditions on the stereochemical outcome of the reaction products. The ratios of diastereomeres were usually determined by NMR-correlation[9] as a mixture of isomers. β-Lactam 6 (run 9-13), however, was converted to the tert. butyldimethylsilylether, which allowed a separation of trans and cis isomers.

In all cases diarylaldimines showed a preference for the formation of trans products (runs 1, 3, 5, 7, 8) when the reaction mixtures were quenched at rt. We observed an excellent stereoselectivity for the formation of trans S* isomers 1a (R = Ph, Ar = Ph; run 1), and 5a (R = furyl, Ar = 3,4,5-trimethoxyphenyl; run 8). Introduction of an N-(p-anisidine) functionality as in 2 and 3 resulted in the formation of a 1:1 mixture of trans S* and trans R* isomers. With increased OMe-substitution at the N-aryl group in the 4-furyl series (run 5, 7, and 8) we obtained larger amounts of the trans S* isomer. The ratios of diastereomeres of 4-vinyl β-lactams were, however, not dependent on the substitution pattern of the N-aryl ring; nor was the stereochemistry of the reaction products dependent on the nature of the vinyl substituent explored (runs 9, 14, 15, 16). We always obtained 7:3 trans-cis ratios of products. The separation of isomers 6 (run 9) revealed a 50:25:25 ratio of 6a, 6b, and 6c respectively. Quenching the reaction mixture at -20°C (run 10) and +10°C (run 11) gave a 50:10:40 mixture of isomers. When the reactions were run without HMPA as a cosolvent (run D and E) we found 1:1 mixtures of 6a and 6c without any trace of 6b (300 MHz NMR). Generally, quenching the reaction mixture at lower temperature (run 4, 6, 9-13) favoured the formation of the cis isomer.[3a] Apparently, the presence of HMPA as well as higher reaction temperatures promote a cis-trans isomerization of the β-lactams (runs 3, 5, 9, 10, 11).

The newly synthesized β-lactams 3-9 carry functional groups at position 4, which will allow further elaboration towards useful chiral carbapenem precursors. Studies directed toward the elucidation of the reaction mechanism as well as the transformation of the newly synthesized β-lactams to useful precursors for the synthesis of carbapenem antibiotics are under way.

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8. All reactions were carried out at a 2 mmol scale. The dianion of ethyl-3-hydroxybutyrate was formed using lithium cyclohexylisopropylamide as a base in THF (5 ml) at -20°C for 1 1/2 h. The imine was either added (procedure A-D) as a solution in THF (2 ml)/HMPA (1.5 equ.) or in THF only (procedure D and E). The reaction time varied between 3 and 5 h after addition of the imine. We quenched the reaction mixtures at rt (procedure A); +10°C (procedures C and D) and at -20°C (procedures B and E). Compounds 1-9 were purified by column chromatography. Their spectroscopic data were in agreement with their structure.
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