218. An Enantioselective β-Lactam Synthesis Starting from L-(*S*)-Glyceraldehyde Acetonide

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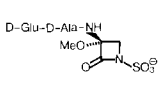
Summary

Complete diastereoselectivity is observed during the cyclocondensation of activated glycine derivatives with aldimines derived from L-(*S*)-glyceraldehyde acetonide. 3,4-*cis*-β-lactams are isolated in high optical and chemical yields. They are converted into key intermediates used in the syntheses of various mono- and bicyclic β-lactam antibiotics. A mechanism is suggested to explain this remarkable diastereoselectivity.

The isolation [1] of the natural *N*-sulfonated monocyclic β-lactam antibiotic **1** and the synthesis of aztreonam **2** – an analog exhibiting an enhanced biological activity [2] – has renewed interest in efficient syntheses of (3*S*)-3-acylamino-4(carbon)-substituted azetidinones **3**. It is of particular interest to find an easy access to *cis*-isomers, since they are in general biologically more active than the corresponding *trans*-isomers [2].



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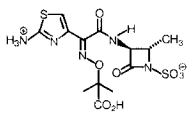

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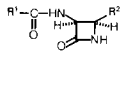

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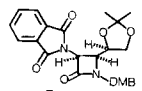

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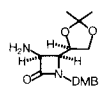

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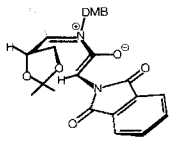

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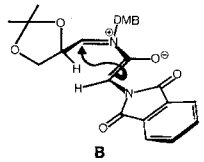

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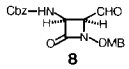

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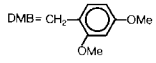

There are only a few reports [3] in the literature of syntheses of such β-lactams which proceed with high stereoselectivity and lead to products of high enantiomeric purity. We wish to present in this communication an enantioselective synthesis of *cis* monocyclic β-lactams based on the classical ketene-imine cycloaddition. The imine component is an optically pure aldimine derived from L-(*S*)-glyceraldehyde acetonide [4].

Thus addition of phthalimidoacetyl chloride to the aldimine **4**[1]) in the presence of Et_3N in CH_2Cl_2 at 0° gave **5**[2]) (m.p. 154°, $[\alpha]_D^{20} = +48.7°$ ($c = 0.6$, $CHCl_3$)) as the sole β-lactam product in 91% yield (HPLC analysis). The enantiomer of **5** (m.p. 155°, $[\alpha]_D^{20} = -49.3°$ ($c = 0.6$, $CHCl_3$)) was obtained in the same conditions and yield using the enantiomer of the aldimine **4** prepared from D-(*R*)-glyceraldehyde acetonide. The ^{1}H-NMR (400 MHz) analysis of azetidinone **5**, in isolated form as well as in the reaction mixture showed only one set of signals when the chiral shift reagent Eu(hfc)$_3$ was added, while a deliberately prepared 2:1 mixture of **5** and its enantiomer gave two distinct sets of signals under the same conditions. Consequently, epimerization at the inducing center of the aldimine **4** during the cycloaddition was ruled out. The relative configuration of the product **5** was established after cleavage of the phthalimido protecting group (NH_2NHCH_3, CH_2Cl_2, 48 h, 25°, 96%). The resulting amine **6** (m.p. 129°C, $[\alpha]_D^{20} = +76.9°$ ($c = 0.7$, CH_3OH)) was shown to have a (3*S*,4*S*)-configuration by X-ray diffraction analysis. Similar results were observed in the cycloaddition of a variety of imines obtained from optically pure α-alkoxy-aldehydes and differently protected glycines (see the *Table*), illustrating the general character of this diastereoselectivity.

Although still a subject of controversy[3]), the mechanism of β-lactam formation from activated glycine derivatives and imines is best rationalized as a non-concerted [2 + 2]-cycloaddition. The first step is the acylation of the aldimine **4** (which exists completely in the (*E*)-configuration [6])[4]) by a ketene, *e.g.* 2-phthalimido-ketene, leading to the zwitterionic intermediate **7**. The second step is a conrotatory ring closure. Applying this mechanism to our case we suggest the following explanation for the remarkable diastereoselectivity. Under the described reaction conditions, no rotation will occur around the double bonds of the iminium [7] and the (*Z*)-enolate groups. There are two rotamers, **A** and **B**, in which the C–O bond at the chiral center is held below or above the plane of the C=N π-bond so that the lone pair of the O-atom interacts through space with the electron deficient iminium π-system. For steric reasons **B** appears to be the preferred conformation of the intermediate zwitterion. Diastereoface selection in the cyclization step is then controlled by attack on the iminium π-system *anti* [8] to the C–O bond in a conrotatory motion.

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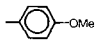
[1]) Prepared from L-(*S*)-glyceraldehyde acetonide and 2,4-dimethoxybenzylamine. $[\alpha]_D^{22} = -12.6°$ ($c = 0.9$, $CHCl_3$).

[2]) All compounds reported were homogenous by TLC and showed ^{1}H-NMR, IR, and MS consistent with assigned structures.

[3]) For a survey of the ketene-imine cycloaddition see [5].

[4]) The (*E*)-configuration of the aldimine **4** was established by measuring the NOE between the benzylic CH_2-protons and the proton of the C=N bond of the imine. Observed NOE: 30%.

Table. *Optically Pure Azetidinones Obtained by Ketene-Imine Cycloaddition*

Compounds	R^1	R^2	R^3	% Yield isolated	$[\alpha]_D^{20}$, c ($CHCl_3$)	m.p.
5			DMB	76	+48.7° (c = 0.6)	155°
9				55	+20.3° (c = 1)[a])	64°
10[b])				72	−88.8° (c = 1)	135°
11[c])			DMB	69	+3.5° (c = 0.1)	145°

[a]) Measured in CH_3OH.

[b]) β-Lactam prepared according to *Bose et al.* [9].

[c]) [*S*]-2-Benzyloxypropionaldehyde was prepared by DMSO-oxalyl chloride oxydation of the corresponding alcohol [10].

Acetonide **6** was easily converted into the aldehyde **8** in over 80% yield (1. $PhCH_2OCOCl$, butylene oxide, CH_2Cl_2, 2. TsOH, THF/H_2O, 80°, 3. $NaIO_4$, CH_3OH). The straightforward synthesis of azetidinone **8** from the key intermediate **5** exemplifies the potential of the reported enantioselective cycloaddition. Similar intermediates have already been used to obtain iso-hetero-cephem skeletons [11]. Aldehyde **8** is also useful for the preparation of 4-substituted *N*-sulfonated monocyclic β-lactam antibiotics.

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