Effective Method for the Asymmetric Synthesis of Bis-β-lactams by the Cycloaddition of Azidoketen to Benzylideneamines Bearing a Chiral β-Lactam Backbone

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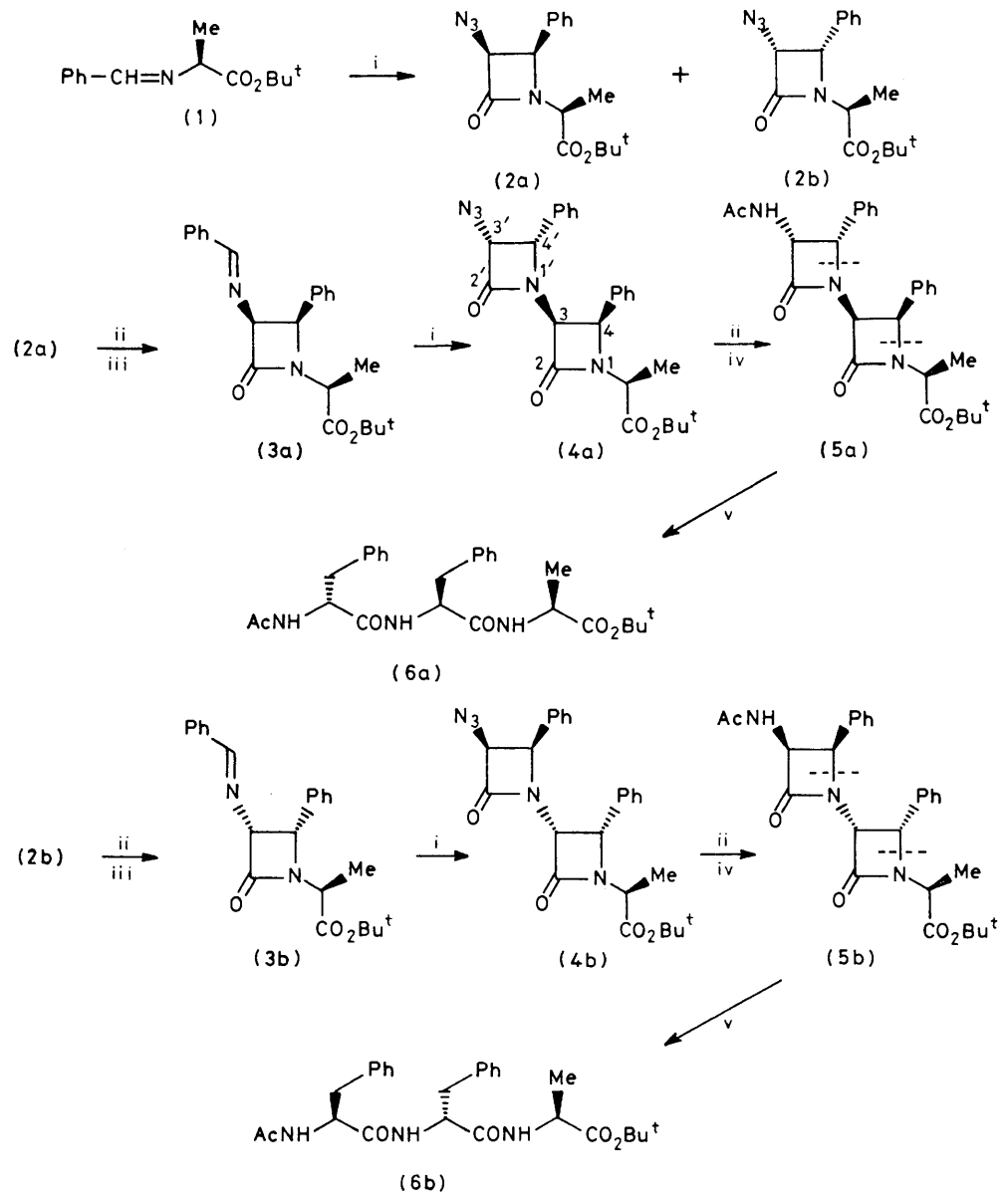
Summary Extremely high stereoselectivity was observed in the asymmetric cycloaddition of azidoketen to 1-[(*S*)-1-t-butoxycarbonylethyl]-3-benzylideneamino-4-phenylazetidin-2-ones, which gave rise to the formation of optically pure bis-β-lactams.

THE formation of β-lactam ring systems has been extensively studied in connection with the synthesis of β-lactam antibiotics, and the addition of keten species to imines is one of the most convenient methods. Although a number of such [2 + 2] cycloadditions have been reported, only a few lead to asymmetric induction.[1-3] We report here the completely stereoselective cycloaddition of azidoketen to imines bearing a chiral β-lactam backbone, and the unambiguous determination of the absolute configuration of the bis-β-lactams produced.

As illustrated in the Scheme, (*S*)-*N*-benzylidene 1-t-butoxycarbonylethylamine (**1**), prepared from t-butyl (*S*)-alaninate and benzaldehyde, was treated with azidoacetyl chloride in the presence of triethylamine in methylene dichloride to give a diastereoisomeric mixture of the β-lactams (**2a**) and (**2b**),† which were readily separated by column chromatography on silica gel (eluant: n-hexane–ethyl acetate, 3:1) and obtained in 39 and 41% yield, respectively. The n.m.r. spectra of both (**2a**) and (**2b**) clearly showed a *cis*-relationship between the 3-azido and 4-phenyl groups ($J_{3,4}$ 5·0 Hz). The azide group in (**2a**) or (**2b**) was converted into NH_2 under 1 atm of hydrogen on Pd–C in methanol at room temperature, and the 3-amino-β-lactams produced were condensed with benzaldehyde to give the 1-[(*S*)-1-t-butoxycarbonylethyl]-3-benzylideneamino-4-phenylazetidin-2-ones (**3a**) (96%) or (**3b**) (96%). Each 3-benzylideneamino-β-lactam was

† All compounds gave satisfactory analytical and spectroscopic data.



SCHEME. Asymmetric synthesis of bis-β-lactams; i, N_3CH_2COCl, Et_3N, CH_2Cl_2, −78 °C to room temperature; ii, H_2 (1 atm), 5% Pd–C, MeOH, room temperature; iii, PhCHO, $MgSO_4$, PhH; iv, Ac_2O, *N*-methylmorpholine, $CHCl_3$; v, H_2 (1 atm), 10% Pd–C, EtOH, 50 °C.

converted into the corresponding bis-β-lactam (**4a**) or (**4b**) by cycloaddition with azidoketen generated *in situ* from azidoacetyl chloride and triethylamine; (**4a**) was obtained from (**3a**) in 74% yield, and (**4b**) from (**3b**) in 48% yield.

In these cycloadditions, only one of the two possible stereoisomers was formed in each case, and none of the other isomer was found in the reaction mixture in spite of the extensive chromatographic work-up on silica gel. The relatively low yield of (**4b**) is mainly due to the low conversion of the reaction.

The newly formed β-lactam ring was proven to have a *cis*-relationship between the 3′-azide and 4′-phenyl groups from the n.m.r. spectra of (**4a**) and (**4b**), which both showed $J_{3',4'}$ 5·0 Hz. However, the absolute configurations of both the β-lactam rings in (**4a**) or (**4b**) remain to be determined. Fortunately, we have recently developed a convenient method for the conversion of 4-aryl-β-lactams into the corresponding peptides by reductive cleavage of the β-lactam ring,[4] and so the absolute configuration of the bis-β-lactams can be unambiguously determined by comparing the peptides derived therefrom with authentic samples. Thus, the azide group in (**4a**) or (**4b**) was reduced to NH_2 and then acetylated to give the *N*-acetyl bis-β-lactams (**5a**) (85%) or (**5b**) (80%). Reductive cleavage of the *N*-acetyl bis-β-lactams (**5a**) and (**5b**) with hydrogen (1 atm) on palladium–carbon at 50 °C gave the corresponding tripeptides. All four of the possible

tripeptides, Ac-(*S*)Phe-(*S*)Phe-(*S*)Ala-OBu^t, Ac-(*R*)Phe-(*S*)-Phe-(*S*)Ala-OBu^t, Ac-(*R*)Phe-(*R*)Phe-(*S*)Ala-OBu^t, and Ac-(*S*)Phe-(*R*)Phe-(*S*)Ala-OBu^t, were prepared independently by unambiguous routes and compared with the tripeptides from bis-β-lactams either spectroscopically or by h.p.l.c. analysis. It was found that Ac-(*R*)Phe-(*S*)Phe-(*S*)Ala-OBu^t was obtained from (**5a**) in 93% yield, and Ac-(*S*)Phe-(*R*)Phe-(*S*)Ala-OBu^t from (**5b**) in 92% yield. Consequently, the stereochemistry of (**4a**) is (3*S*,4*R*,3′*R*,4′*S*), and that of (**4b**) (3*R*,4*S*,3′*S*,4′*R*). In both cases, the second β-lactam ring has the opposite configuration to the first one.

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