Novel and Effective Routes to Optically Pure Amino Acids, Dipeptides, and Their Derivatives *via* β-Lactams obtained through Asymmetric Cycloaddition

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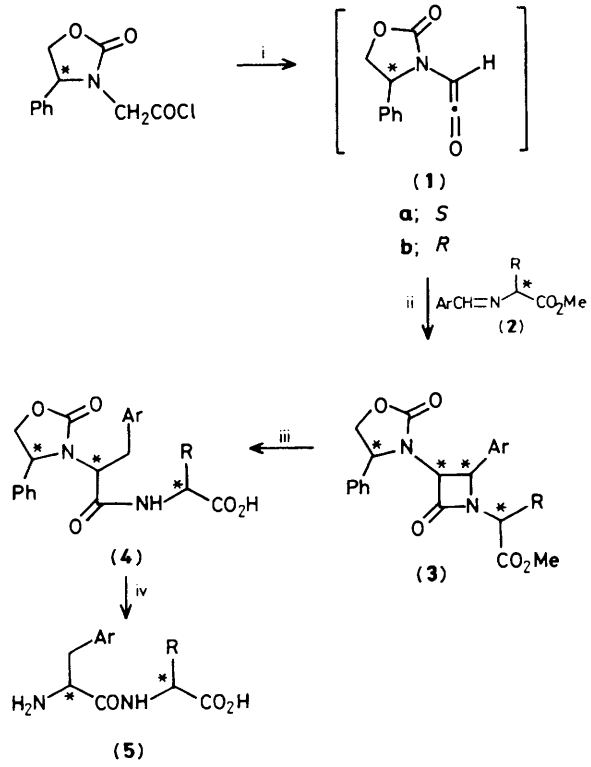
Optically pure dipeptides bearing aromatic amino acid residues were synthesized *via* homochiral (optically pure) β-lactams which were obtained through asymmetric cycloadditions of homochiral ketenes to homochiral imines.

In recent years, the β-lactam skeleton has been recognized as providing useful synthetic building blocks by exploiting its strain energy, in addition to its use in the synthesis of a variety of β-lactam antibiotics.[1,2] We have been developing such new aspects of β-lactam chemistry using homochiral (optically pure) β-lactams as versatile intermediates for synthesis of aromatic amino acids and their derivatives,[3] oligopeptides,[4] and azetidines which are further converted into homochiral polyamines, polyamino alcohols, and polyamino ethers.[5] Our 'β-lactam synthon method' has been successfully applied to the chiral synthesis of enkephalin analogues.[6]

However, our previous syntheses were based on homochiral diastereoisomeric β-lactams which were obtained through chromatographic separations of two diastereoisomers since only cycloadditions of achiral ketenes such as azidoketene, phenoxyketene, and benzyloxyketene to chiral imines were employed. Recently, it has been shown that the asymmetric cycloaddition of chiral ketenes to achiral imines can yield β-lactams with good to excellent stereoselectivity by Ikota and Hanaki,[7] and Evans and Sjogren.[8] These reports led us to examine the applicability of chiral ketenes to the reaction with chiral imines in which favourable and unfavourable double asymmetric inductions need to be taken into account. If the asymmetric cycloaddition can achieve excellent stereoselectivity regardless of the chiral centres in the imines, the process will provide extremely effective routes to the direct precursors of homochiral dipeptides and azetidines with desired configurations. We now describe new and effective asymmetric syntheses of peptides *via* homochiral β-lactams.



Scheme 1. *Reagents and conditions:* i, NEt_3, CH_2Cl_2, −78 °C; ii, CH_2Cl_2, −78 to 0 °C, 2 h; iii, (a) 1 M NaOH–THF, room temp., 1 h, (b) H_3O^+, (c) H_2, Pd/C, MeOH, 50 °C, 5 h; iv, Li–NH_3–THF–Bu^{t}OH, −78 °C, 15 min.

First, we looked at the effectiveness of asymmetric induction by homochiral ketenes ('Evans–Sjogren ketenes') generated *in situ* from homochiral phenyloxazolidinylacetyl chloride [(**1a**), *S*; (**1b**), *R*] in the [2 + 2] cycloaddition to homochiral imines (**2**) derived from esters of alanine, valine, phenylalanine, and methionine.† As shown in Table 1, the chiral centres in the imines (**2**) fortunately do not have any significant influence on the asymmetric induction and no appreciable double asymmetric induction is observed, *viz.*, the chiral centre in the ketene (**1**) only plays a key role in this asymmetric synthesis.

The synthesis of the (3*R*,4*S*)-β-lactam (**3e**) from (**1b**) and (**2e**; R = $PhCH_2$) is typical. To (**1a**) (1.0 mmol) in CH_2Cl_2 (10 ml) was added Et_3N (1.8 mmol) at −78 °C. The solution was stirred for 15 min, and (**2e**) (1.2 mmol) in CH_2Cl_2 was added. The mixture was allowed to warm to 0 °C during 2 h, and then quenched with water. After the usual work-up and chromatographic purification, (**3e**) was obtained as a colourless solid (91% yield, 100% diastereoisomeric excess by h.p.l.c.).

The β-lactams (**3**) thus obtained were saponified, converted into the corresponding *N*-protected dipeptides (**4**) quantitatively through hydrogenolysis over Pd/C in MeOH, and submitted to Birch reduction with Li in liquid NH_3–tetrahydrofuran (THF)–Bu^{t}OH to give the corresponding homochiral dipeptides (**5**) in excellent yields.‡

Table 1. Asymmetric [2 + 2] cycloadditions of homochiral ketenes (**1**) to homochiral imines (**2**).

Entry	Ketene (**1**)	Imine: R in (**2**) and configuration	Yield (%)	β-Lactam (**3**)[a] M.p./°C	$[\alpha]_D^{20}$/°[b]
a	(**1a**)	Me (*S*)	76	150—152	+22.1 (*c* 1.0)
b	(**1a**)	Me (*R*)	82	174—175	+29.5 (*c* 2.7)
c	(**1b**)	Pr^i (*S*)	92	161—162	−58.8 (*c* 1.6)
d	(**1b**)	Pr^i (*R*)	86	159—160	−16.9 (*c* 1.3)
e	(**1b**)	$PhCH_2$ (*S*)	91	170—172	−48.4 (*c* 1.8)
f	(**1b**)	$MeS[CH_2]_2$ (*S*)	79	120—122	−37.1 (*c* 2.3)

[a] All β-lactams are *cis* based on the $J_{3,4}$ values (5.0—5.2 Hz). [b] Measured in $CHCl_3$.

† Despite an extensive search by h.p.l.c. and n.m.r spectroscopy, the other diastereoisomer of (**3**) could not be detected in any case examined.

‡ H.p.l.c. analysis (Waters C18 Bondapak column, MeOH–H_2O–NH_4OAc) of the dipeptide thus obtained showed a single peak (>99.5% diastereoisomeric excess) corresponding to that of the authentic sample in every case examined, which clearly indicated that no racemization took place during the process.

Typically, (**3c**) (0.44 mmol) was saponified with 1 M NaOH followed by hydrogenolysis (1 atm H_2) over 5% Pd/C (0.44 mmol) in MeOH (10 ml) at 50 °C for 5 h to give (**4c**) in 95% yield. The Birch reduction of (**4c**) (0.44 mmol) was carried out with Li (3.5 mmol) in liquid NH_3 (15 ml), THF (5 ml), and Bu^tOH (3.5 mmol) at −78 °C for 15 min. The reaction was quenched with solid NH_4Cl. After the usual work-up, (*R*)-Phe-(*S*)-Val-OH was obtained in 97% yield (h.p.l.c.).‡

Since it is demonstrated that (i) the required absolute configurations can be introduced into the chiral β-lactams (**3**) regardless of the chiral centres in the imines, and (ii) no racemization is observed during Birch reduction, the asymmetric cycloaddition–reductive cleavage process should provide an effective route to homochiral dipeptides, which are particularly useful for the introduction of unnatural amino acid residues with desired absolute configurations into physiologically active peptides.

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