SYNTHETIC STUDIES ON OPTICALLY ACTIVE β-LACTAMS.[1] ASYMMETRIC SYNTHESIS OF β-LACTAMS BY THE CYCLOCONDENSATION UTILIZING CHIRAL HETEROCYCLIC COMPOUNDS DERIVED FROM L-(+)-TARTARIC ACID AND (S)-GLUTAMIC ACID

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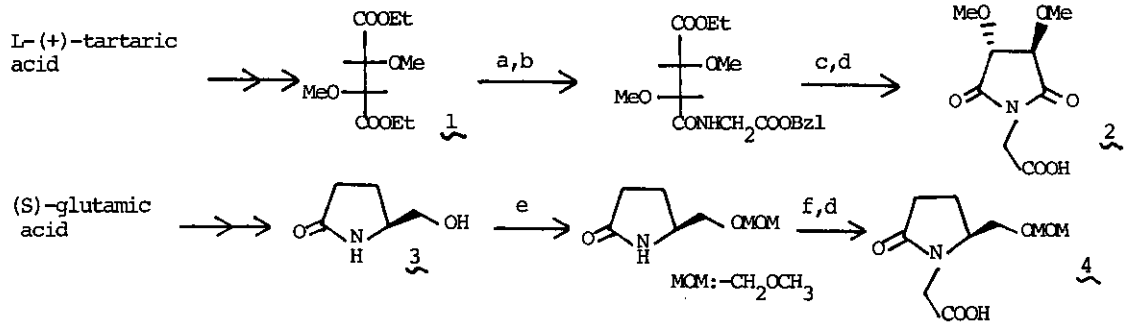
Abstract——— Asymmetric cyclocondensation of the chiral heterocyclic compounds (2,4) with imines (5) gave either cis- or trans-β-lactams with high diastereomeric purity up to 96%, and the optically pure phenylalanine derivative (9) was obtained from the β-lactams produced.

The chiral synthesis of β-lactam ring systems has been extensively studied, and the common procedure for preparing β-lactams is the cyclocondensation of a ketene species with an imine. Although several asymmetric syntheses of β-lactams by the [2+2] cyclocondensation were reported,[2] there have been no application of chiral ketene species to the asymmetric β-lactam formation.[3] Here, we describe our studies on models for a highly diastereoselective cyclocondensation of activated glycine derivatives bearing the chiral heterocycles derived from L-(+)-tartaric acid and (S)-glutamic acid as ketene species.

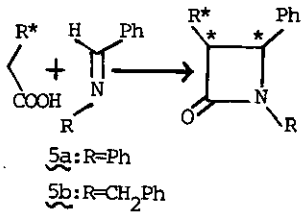
As illustrated in Scheme 1, the chiral tartarimide derivative[4] (2, mp 60°C, $[\alpha]_D^{20}$ +172°(c=0.8,$CHCl_3$)) and the chiral 2-pyrrolidinone derivative (4, $[\alpha]_D^{20}$ +6.2° (c=2,EtOH)) were prepared from (+)-diethyl dimethoxysuccinate (1)[5] and (S)-5-hydroxymethyl-2-pyrrolidinone (3)[6] in 40% and 45% yields, respectively. Compounds 2 and 4 (1.3 eq.) were converted into the corresponding mixed anhydrides with trifluoroacetic anhydride,[7] and were condensed with imines (5) in the presence of triethylamine in methylene chloride for 20 h to afford the β-lactams as a mixture of diastereomers. Each isomer was separated by column

Scheme 1



Reagents: (a) aq.NaOH(1 eq.), (b) Gly-OBzl·p-TsOH, $(EtO)_2P(O)CN$, TEA, (c) Na powder, toluene, (d) H_2/Pd-C, (e) MOMCl, N,N-diethylaniline, (f) NaH, $BrCH_2COOBzl$, THF.

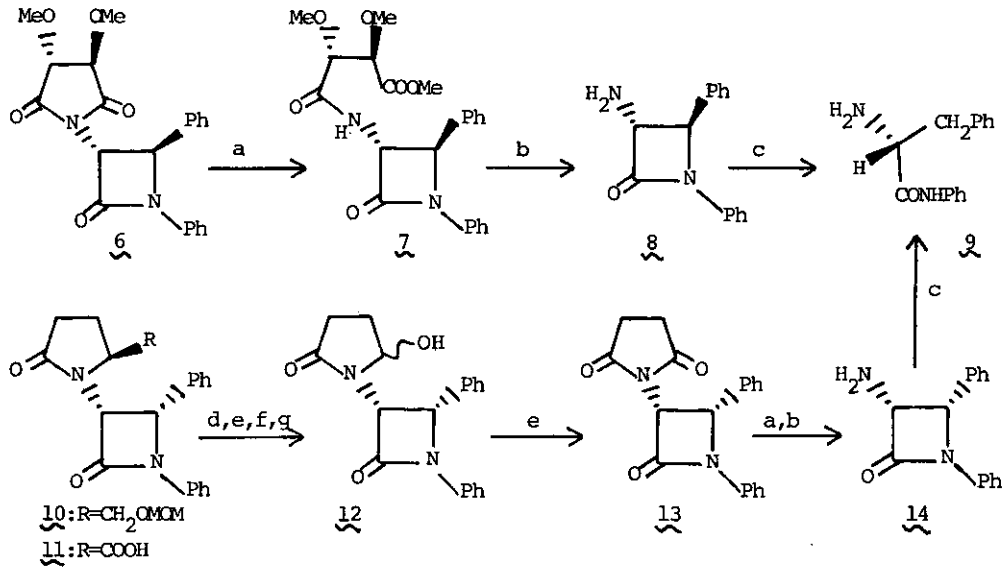
Table Asymmetric Induction in the β-Lactam Formation



Reagent	Reaction Temp. (°C)	Imine	Yield (%)	cis/trans	Ratio of diastereomers	Asymmetric induction (%)
2	0	5a	47	0/100	84/16 a)	68
2	-20	5a	40	0/100	87/13 a)	74
4	0	5a	71	86/14 b)	97/3 c)	94
4	-20	5a	62	84/16 b)	98/2 c)	96
4	0	5b	55	95/5 b)	95/5 c)	90

a) Ratio of the trans-diastereomers.
b) The minor diastereomer of the trans-β-lactam was not detected.
c) Ratio of the cis-diastereomers.

Scheme 2



Reagents: (a) NaOMe(1 eq.), MeOH, (b) PCl_5, pyridine, CH_2Cl_2; MeOH; H^+, (c) H_2/10% Pd-C, EtOH, (d)10% HCl,MeOH,55°,(e) Jones reagent, (f) $Pb(OAc)_4$, DMF, AcOH, (g) 50% AcOH, 50°.

chromatography on silica gel ($CHCl_3$:AcOEt:Hex.=10:1:1 or $CHCl_3$:AcOEt=5:1 as eluent), and the ratio of the isomers was calculated by HPLC. Summarized results were listed in the Table. Employing the reagent 2, trans-β-lactams($J_{3,4}$=2 Hz) were formed with 74 % asymmetric induction. On the other hand, cis-β-lactams($J_{3,4}$=5 Hz) were predominantly formed with high diastereoselectivity (up to 96 % de) using the reagent 4.

The chiral auxiliaries in the β-lactams produced were successfully removed leaving the β-lactam ring intact to afford 3-amino-2-azetidinone derivatives as follows (Scheme 2). The isolated major diastereomer 6 (mp 233°C, $[\alpha]_D^{20}$ +188°(c=0.4, $CHCl_3$)) was treated with sodium methoxide (1 eq.) in methanol to give the amide derivative (7), and the selective cleavage of the amide bond via methyl imino ether (PCl_5,pyridine,CH_2Cl_2; MeOH; H^+) gave trans-3-amino-1,4-diphenyl-2-azetidinone (8, $[\alpha]_D^{20}$ -74°(c=0.5,$CHCl_3$)) in 40 % yield with the recovery of (+)-dimethyl dimethoxysuccinate. Successive treatments of 11, prepared from the major diastereomer 10 (mp 183°C, $[\alpha]_D^{20}$ +34°(c=0.4,$CHCl_3$)) by MOM group cleavage and Jones oxidation, with lead tetraacetate (DMF-AcOH) and 50% aqueous acetic acid introduced the hydroxy group at the C_5-position of the 2-pyrrolidinone moiety. The imide derivative (13) obtained from 12 by Jones oxidation was treated under the same conditions as described above to provide cis-3-amino-1,4-diphenyl-2-azetidinone (14, mp 209°C, $[\alpha]_D^{20}$ +193°(c=0.84,$CHCl_3$)) in 42 % yield from 10. Since the optically pure (R)-phenylalanine derivative (9, mp 63°C, $[\alpha]_D^{20}$ +138° (c=0.3,$CHCl_3$), identical with an authentic sample of (R)-9) was obtained from 8 and 14 by N-C_4 bond cleavage,[8] the asymmetric synthesis of phenylalanine was also attained, and the absolute configurations of the newly formed asymmetric carbons were determined as (3R,4R) for 8 and (3R,4S) for 14.

The method described here using the chiral reagents 2 and 4 might be highly stereoselective and provides a versatile synthesis of the chiral β-lactam ring systems. Further synthetic studies on optically active β-lactams using these reagents are under investigation.

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