

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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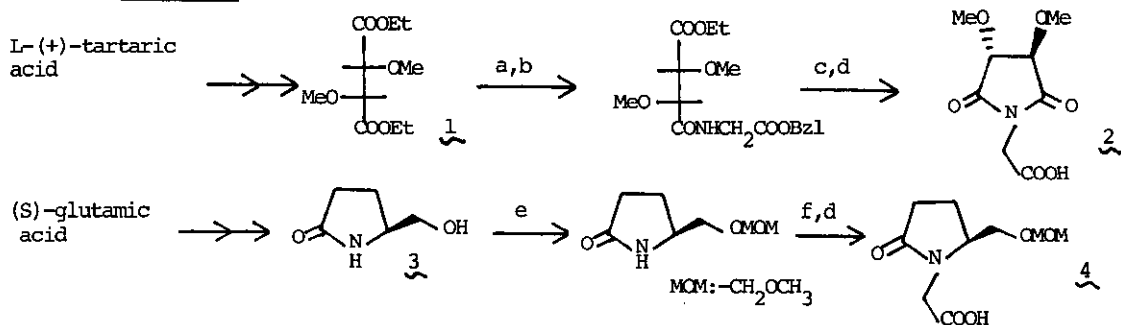
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Abstract—— Asymmetric cyclocondensation of the chiral heterocyclic compounds (2,4) with imines (5) gave either cis- or trans- β -lactams with high diastereomeric purity up to 96%, and the optically pure phenylalanine derivative (9) was obtained from 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 derivative⁴ (2, mp 60°C, $[\alpha]_D^{20} +172^\circ$ (c=0.8, CHCl₃)) and the chiral 2-pyrrolidinone derivative (4, $[\alpha]_D^{20} +6.2^\circ$ (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

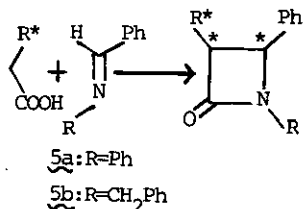
Scheme 1



Reagents: (a) aq. NaOH (1 eq.), (b) Gly-OBzl·p-TsOH, $(\text{EtO})_2\text{P}(\text{O})\text{CN}$, TEA, (c) Na powder, toluene, (d) $\text{H}_2/\text{Pd-C}$, (e) MOMCl, *N,N*-diethylaniline, (f) NaH, $\text{BrCH}_2\text{COOBzl}$, THF.

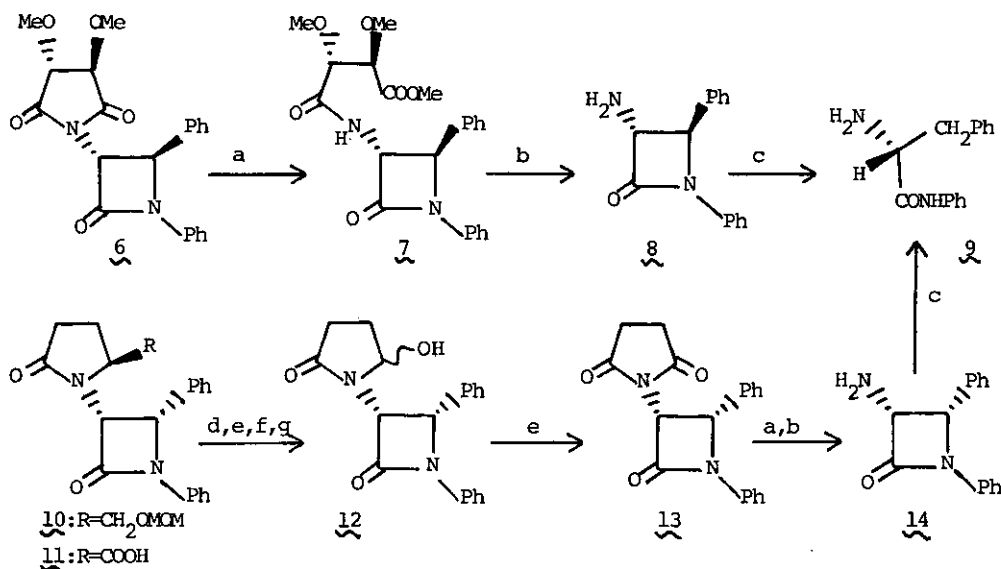
Table Asymmetric Induction in the β -Lactam Formation

Reagent	Reaction Temp. (°C)	Imine	Yield (%)	cis/trans Ratio	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) $\text{H}_2/10\% \text{Pd-C}$, EtOH, (d) 10% HCl, MeOH, 55%, (e) Jones reagent, (f) $\text{Pb}(\text{OAc})_4$, DMF, AcOH, (g) 50% AcOH, 50°.

chromatography on silica gel ($\text{CHCl}_3:\text{AcOEt}:\text{Hex.}=10:1:1$ or $\text{CHCl}_3:\text{AcOEt}=5:1$ 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, $[\alpha]_D^{20} +188^\circ$ (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, $[\alpha]_D^{20} -74^\circ$ (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, $[\alpha]_D^{20} +34^\circ$ (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, $[\alpha]_D^{20} +193^\circ$ (c=0.84, CHCl_3)) in 42 % yield from 10. Since the optically pure (R)-phenylalanine derivative (9, mp 63°C, $[\alpha]_D^{20} +138^\circ$ (c=0.3, CHCl_3), identical with an authentic sample of (R)-9) was obtained from 8 and 14 by N-C₄ 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.

ACKNOWLEDGMENT

The authors are grateful to Prof. T. Hino and Prof. S. Sakai of Chiba University for spectral measurements.

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Received, 8th June, 1984