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Synthesis of Optically Pure 4-Cyano and 4-Formyl *cis*-β-Lactams via Enantiospecific Staudinger Reaction#

M. Jayaraman, M. Nandi, K.M. Sathe, A.R.A.S. Deshmukh and B.M. Bhawal*

Division of Organic Chemistry: Synthesis
National Chemical Laboratory, Pune 411 008, India.

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Abstract: *Imines* **1** *&* **2** *derived from (+)-(1S,2S)-2-amino-1-phenylpropan-1,3-diol on cycloaddition reaction using acid chlorides (or equivalent)* **3-6** *in the presence of triethylamine furnished stereoselectively cis-β-lactams* **7a-f** *in good yields. The aminols* **8b,c** *on treatment with lead tetraacetate under different reaction conditions gave 4-cyano* (**9b,c**) *and 4-formyl* (**10b,c**) *β-lactams in high yields.*

Homochiral β-lactams can provide facile entries to important biologically active compounds, besides β-lactam antibiotics.[1] Enantiospecific syntheses of β-lactams using chiral starting materials (e.g.) homochiral aldehydes with an α stereogenic centre[3] in the Staudinger reaction have been widely exploited to this end.[2] When the α carbon is attached to a heteroatom a very high degree of diastereoselectivity is attained[4], though we have recently demonstrated that it is not a mandatory requirement for high stereoselection.[5] A practical synthesis demands that an inexpensive starting material be utilized without impairing the diastereoselectivity of the process.

We wish to report that (+)-(1S,2S)-2-amino-1-phenylpropan-1,3-diol meets this requirement and provides ready access to variously substituted homochiral *cis*-β-lactams. This aminodiol is the unwanted product in chloramphenicol synthesis and is readily available in optically pure form. Furthermore the aminol moiety in the homochiral starting material can be exploited to synthesise both 4-cyano and 4-formyl derivatives independently by suitable manipulation of reaction conditions.

The imines **1** & **2** were prepared[6] from (+)-(1S,2S)-2-amino-1-phenylpropan-1,3-diol.[7] The reaction of imines **1** & **2** with acid chlorides **3-5** in the presence of excess triethylamine (-20°C to r.t., 20h) gave *cis*-β-lactams (**7a-c,e,f**) in very good yields[8] (**Scheme 1**). *In all the cases a single diastereomer was obtained* (no trace of other isomer could be detected in the 200MHz ^{1}H NMR and HPLC analysis of the crude reaction mixture). The synthesis of azido β-lactam **7d** was carried out by Bose's mixed anhydride method using cyanuric chloride[3b] at -20°C.

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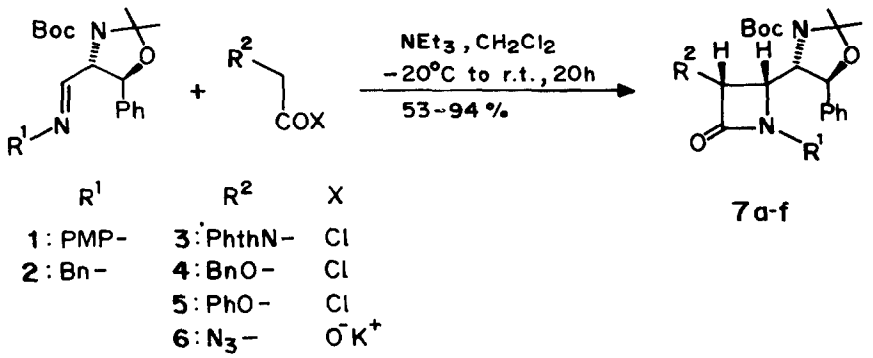
Scheme-1



R^1	R^2	X
1 : PMP-	3 : PhthN-	Cl
2 : Bn-	4 : BnO-	Cl
	5 : PhO-	Cl
	6 : N_3-	O^-K^+

Table. Cycloaddition reaction between ketene derived from precursors **3-6** and imines **1** & **2**.

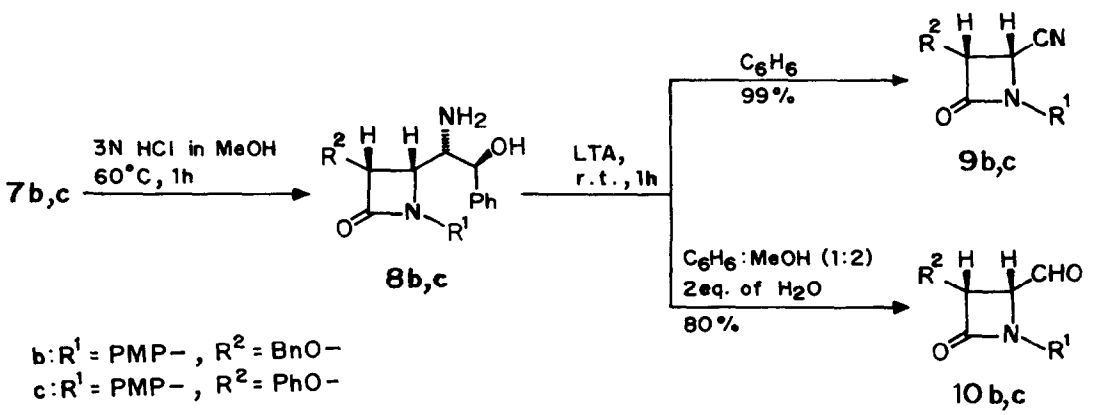
Compd 7	R^1	R^2	Yield[a] %	m.p. °C	$[\alpha]_D$ (c 1, $CHCl_3$)	$J_{3,4}$, Hz[b]
a	PMP-	PhthN-	73	235-236	-90.1	5.5
b	PMP-	BnO-	91	oil	+47.9	5.4
c	PMP-	PhO-	74	145-146	+86.7	5.2
d	PMP-	N_3-	53	oil	+86.6	5.9
e	Bn-	PhthN-	91	174-175	-138.4	5.2
f	Bn-	PhO-	94	65-67	-29.2	5.0

a: Isolated yields of pure β-lactams after column purification.

b: Coupling constant of C3-H doublet indicating the *cis*-β-lactam stereochemistry.

PhthN- = *phthalimido*; **PMP-** = *p-methoxyphenyl*. **Bn-** = *benzyl*.

Scheme-2



Treatment of the β-lactams **7b,c** with 3N HCl in MeOH at 60°C for 1h provided the N,O deprotected aminols **8b,c** in quantitative yield (**Scheme 2**). Surprisingly, the aminols **8b,c** on treatment with lead tetraacetate under the reported conditions[3e] (benzene, r.t., 1h) resulted in the formation of the 4-cyano compounds[9] **9b,c** in quantitative yield instead of the expected 4-formyl β-lactams. However, the aminols **8b,c** on treatment with lead tetraacetate in benzene : methanol (1:2) in the presence of 2 equivalents of water gave exclusively 4-formyl β-lactams **10b,c** in 80% yield. These 4-formyl-β-lactams are known to be efficient precursors[10,11] for PS5, PS6, thienamycin and β-hydroxy aspartates.

The relative configurations within the β-lactam **7a**[12] was established from single crystal X-ray diffraction analysis.[13] The configurations at C3 and C4 of the β-lactam **7a** were assigned as **3R,4S** on the basis of the known absolute configuration **4'S,5'S** of the aminol moiety (**Fig 1**). The absolute configuration of **7b** was confirmed by converting it to the known 4-formyl β-lactam **10b** [obs.$[\alpha]_D$ = +178.6 (c = 1, CH_2Cl_2); lit.[3e] $[\alpha]_D$ = +179.2 (c = 1, CH_2Cl_2)].

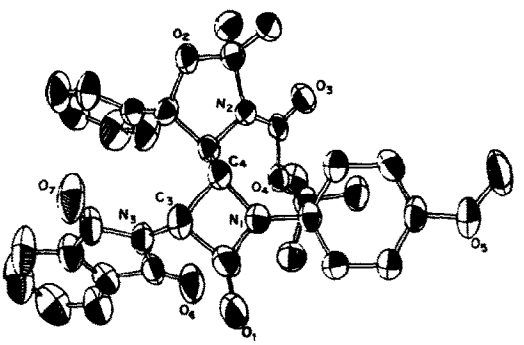


Fig. 1. **ORTEP** diagram of **7a**

In conclusion, we have shown that the synthesis of various homochiral β-lactams can be achieved by using an inexpensive starting material, (+)-(1S,2S)-2-amino-1-phenylpropan-1,3-diol. We have also shown that varying the reaction conditions of the lead tetraacetate oxidation, 4-cyano and 4-formyl β-lactams can be prepared.

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1. a) Manhas, M.S.; Wagle, D.R.; Chiang, J.; Bose, A.K. *Heterocycles*, **1988**, *27*, 1755; b) Palomo, C.; Arrieta, A.; Cossio, F.P.; Aizpurua, J.M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.*, **1990**, *31*, 6429.
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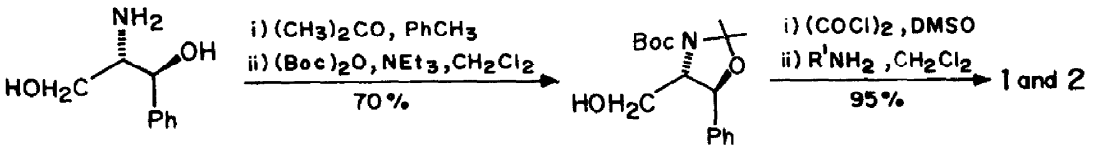
6. The imines **1** & **2** were prepared in good yields by the following Scheme.



7. The starting material supplied by Parke Davis was crystalized before use and its optical purity was confirmed by specific rotation $[\alpha]_D$ = +38 (c 1, 1N HCl); *Beil.* **13**, *4*, 2698.
8. In a typical procedure, a solution of the acid chloride (15 mmol) in anhydrous methylene chloride (30 mL) was slowly added to a solution of the Schiff's base (10 mmol) and triethylamine (50 mmol) in methylene chloride (30 mL) at -20°C. The resulting mixture was allowed to warm up to room temperature and stirred for 20h. The reaction mixture was then successively washed with water (2 X 30 mL), satd. $NaHCO_3$ (2 X 30 mL) and water (30 mL). The organic layer was dried (Na_2SO_4), and concentrated to give the crude product, which was then column chromatographed to give β-lactams (**7a-f**) in 53-94% yield.
9. **9b**: m.p. 130-131°C ($CHCl_3$/n-hexane); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45-7.25(m, 7H), 6.85(d, J = 9Hz, 2H), 5.00(d, J = 5Hz, 1H), 4.80(s, 2H), 4.65(d, J = 5Hz, 1H), 3.75(s,3H); **^{13}C NMR**: 47.95, 55.68, 73.92, 82.16, 114.26, 114.95, 118.66, 128.74, 128.87, 129.36, 135.67, 157.60, 161.30; **IR** ($CHCl_3$): 2260, 1770, 1620 and 1590 cm^{-1}. **MS**(*m/z*): 308(M^+). Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.10, H, 5.23, N, 9.08. Found: C, 70.30, H, 5.48, N, 9.21. $[\alpha]_D$ = +140.2 (c = 1, $CHCl_3$).
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12. **7a**: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.70-7.50(m, 6H), 7.05-6.75(m, 7H), 5.55(d, J = 5Hz, 1H), 5.25(dd, J = 2 & 12Hz, 1H), 4.80-4.70(m, 2H), 3.80(s, 3H), 1.80(s, 3H), 1.35(s, 3H), 1.15(s, 9H); **^{13}C NMR**: 27.49, 27.90, 29.29, 55.42, 55.76, 60.93, 61.53, 79.83, 81.03, 96.88, 114.68, 118.50, 123.42, 127.10, 128.21, 128.49, 131.28, 132.33, 134.14, 138.58, 151.91, 156.80, 161.11, 167.27; **IR** (Nujol): 1770, 1730, 1620, 1600 and 1520 cm^{-1}. **MS**(*m/z*): 597(M^+). Anal. Calcd. for $C_{34}H_{35}N_3O_7$: C, 68.30, H, 5.90, N, 7.00. Found: C, 67.84, H, 6.21, N, 6.97. $[\alpha]_D$ = -90.1 (c = 1, $CHCl_3$).
13. X-Ray Determination of (**7a**): Data were measured on an Enraf-Nonius CAD4 diffractometer with Mo-Kα radiation at 300°K. Cell dimensions: a = 9.735(2), b = 15.402(1), c = 11.233(6) A°, α = γ = 90°, β = 112.39(3)°; V = 1557.1(9)A^{03}, Z = 2, dcalc = 1.275$Mg.m^{-3}$, μ = 0.08mm^{-1}, monoclinic, Space group $P2_1$, data collection of 2396 unique intensities, ($2\theta_{max}$ = 46.9°), 2093 observed, [I > 2.5 σ(I)],. The structure was solved using SHELX-86[14a] package and refinement was done using NRCVAX package,[14b] with full matrix least squares, 396 parameters, hydrogen atoms were placed at idealized position with fixed isotropic temperature factors (U = 0.4A^2), R = 0.052, R_w = 0.050.
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