Efficient Asymmetric Synthesis of *cis*-4-Formyl β-Lactams from L-(+)-Tartaric Acid†,‡

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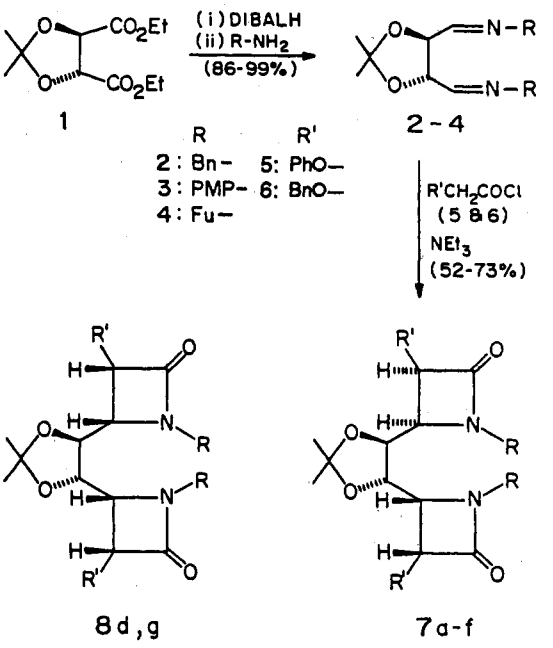
cis-4-Formylazetidin-2-ones are versatile building blocks for the synthesis of monobactams, isocephams, carbapenems, and non-β-lactam products like β-hydroxy aspartates and hydroxybutanoic acids.[1] Recently, there has been a renewed interest in the stereoselective synthesis of such compounds.[1e,2] However, there are only a limited number of methods available for the enantiospecific synthesis of *cis*-4-formyl β-lactams.[3]

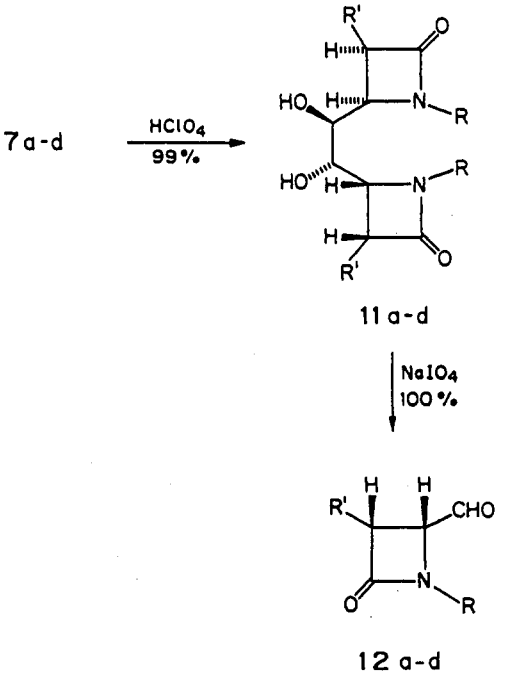
In pursuance of our studies[4] in asymmetric synthesis of β-lactams, we report an efficient asymmetric synthesis of novel C_2 symmetric bis-β-lactams and their near-quantitative conversion to optically pure 4-formyl-β-lactams of known absolute configuration. Tartaric acid derivatives have been utilized as *chiral auxiliaries* as well as a *chiron* for the synthesis of β-lactams.[5] The present work exploits the C_2 symmetry of natural tartaric acid to achieve the synthesis of 2 mol of homochiral *cis*-4-formyl β-lactams from 1 mol of tartaric acid.

(4*R*,5*R*)-(−)-Diethyl 2,3-*O*-isopropylidene-L-tartarate (**1**) was prepared from L (+)-tartaric acid using a reported procedure.[6] Diimines **2–4** were prepared from **1** in two steps in one pot by reduction with DIBALH followed by treatment with amines. The diimines **2–4** on annelation with acid chlorides **5** and **6** in the presence of excess triethylamine (−23 °C to rt, 14 h) gave C_2 symmetric β-lactams **7a–f** in good yields (Scheme 1). In the case of diimines **2** and **4** the formation of diastereomer **8** in small amounts (<5%) was also observed which could not be isolated in pure form. However, the major diastereomer **7** can be easily separated by column chromatography. The imine **3**, when reacted with acid chloride **6** in the presence of excess of Et_3N at 0 °C, gave a mixture of **7d**:**8d** (70:30) in 81% yield from which pure diastereomers **7d** and **8d** were isolated by column chromatography. Hence, the reaction temperature (−23 °C) is crucial for optimum yield with high diastereoselectivity.

Scheme 1



Scheme 2



Treatment of the β-lactams **7a–d** with $HClO_4$ in THF at rt for 4–8 h provided the deprotected dihydroxy β-lactams **11a–d** in quantitative yields. These dihydroxy compounds on treatment with $NaIO_4$ under usual conditions[3c] afforded homochiral *cis*-4-formyl β-lactams **12a–d** in quantitative yields (Scheme 2). The quantitative conversion of diol **11c** to **12c** can also be effected by using

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(7) Under similar conditions the bulky phthalimidoglycyl chloride gave only *cis*-mono-β-lactam even with 4 equiv of acid chloride.

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Table 1. Synthesis of β-Lactams 7a-f and 8g and the Deprotected Diols 9d,g and 11a-d

compd	R	R′	yield[a] (%)	mp (°C)	$[\alpha]_D$
7a	Bn-	PhO-	61	120-121	+141.8
7b	Bn-	BnO-	53	oil	+73.6
7c	PMP-	PhO-	73	125-127	+171.8
7d	PMP-	BnO-	52	70-72	+90.7
7e	Fu-	PhO-	63	136-138	+152.6
7f	Fu-	BnO-	58	oil	+49.5
8g	PMP-	MeO-	62	oil	+18.0
9d	PMP-	BnO-	99	203-205	+31.6
9g	PMP-	MeO-	99	189-191	+29.7
11a	Bn-	PhO-	99	165-167	+151.9
11b	Bn-	BnO-	99	150-151	+73.6
11c	PMP-	PhO-	98	oil	+149.9
11d	PMP-	BnO-	97	168-169	+140.6

[a] Isolated yields of pure β-lactams after column purification. PMP- = *p*-methoxyphenyl; Bn- = benzyl; Fu- = furfuryl.

Table 2. Synthesis of *cis*-4-Formyl β-Lactams 12a-d and 10d,g

compd	R	R′	yield[a] (%)	mp (°C)	$[\alpha]_D$ (lit.$[\alpha]_D$)
12a	Bn-	PhO-	98	oil	+57.6
12b	Bn-	BnO-	99	114-115	+86.2 (+85.9)[3c]
12c	PMP-	PhO-	99	138-139	+173.5 (+173.4)[4b]
12d	PMP-	BnO-	99	154-155	+178.5 (+178.6)[4b]
10d	PMP-	BnO-	99	126-127	0.0
10g	PMP-	MeO-	99	100-102	0.0

[a] Isolated yields of pure β-lactams after column purification. PMP- = *p*-methoxyphenyl; Bn- = benzyl.

an excess of lead tetraacetate in benzene under usual conditions.[8]

The formation of one diastereomer as the major product, using diimines derived from L-(+)-tartaric acid, indicates the remarkable stereoselectivity of the Staudinger reaction, as this involves the formation of two β-lactam rings in a single operation with high yield and excellent stereocontrol. The absolute configuration of the β-lactams **7a-f** were expected to be 3′*R*,4′*S* from the earlier report[3c] and was confirmed by comparing the rotations of the 4-formyl β-lactams **12b-d**, obtained from **7b-d**, with the compounds of known absolute configuration[3c,4b] (see Table 2).

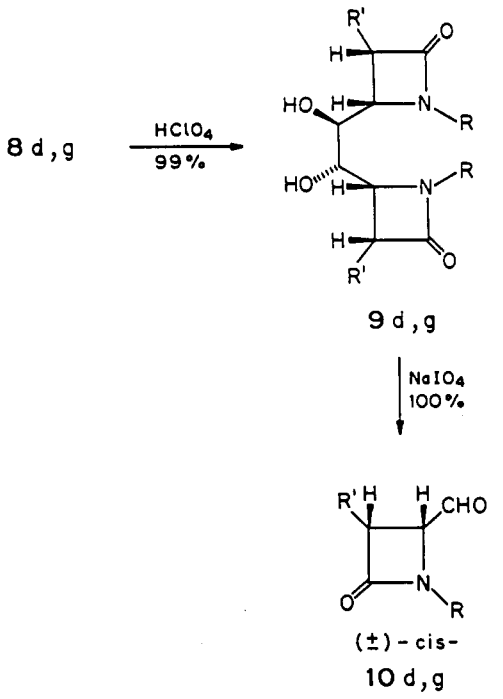
Surprisingly, the treatment of methoxyacetyl chloride with diimine **3** at −23 °C gave diastereomer **8g** as the sole product in 62% yield.[7] The diastereomers **8d** and **8g** showed two sets of signals in ^{1}H NMR spectrum which reveals the disymmetry of the molecule. Treatment of **8d** and **8g** with $HClO_4$ provided diols **9d** and **9g** in quantitative yields. These diols on periodate cleavage gave racemic *cis*-4-formyl β-lactams **10d** and **10g** in quantitative yield (Scheme 3). The formation of the racemic *cis*-4-formyl β-lactam as the sole product from the diols **9d** and **9g** confirms the assigned absolute configuration 3′*R*,4′*S*,3″*S*,4″*R*.

In conclusion, we have developed a simple and convenient method for building *cis*-4-formyl β-lactams in excellent chemical and optical yields from cheap and readily available L-(+)-tartaric acid. The other enantiomer of **12**, more useful for the preparation of bicyclic β-lactams of natural C-4 configuration, can also be prepared using this methodology as D-(−)-tartaric acid is also commercially available.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 spectrometer at 200 and 50 MHz, respectively.

Scheme 3



The ^{1}H chemical shifts are reported in ppm downfield from tetramethylsilane. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer Model 599-B using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and are uncorrected. Mass spectra were determined on a Finnigan Mat-1020 spectrometer, and microanalyses were performed on a Carlo-Erba 1100 automatic analyzer. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. Methylene chloride was distilled over P_2O_5, and toluene was freshly distilled over potassium-benzophenone ketyl under argon. Silica gel (SD's, 60-120 mesh) was used for column chromatography.

General Procedure for the Synthesis of Diimines 2-4. To a solution of (4*R*,5*R*)-(−)-diethyl 2,3-*O*-isopropylidene-L-tartarate[6] (10 mmol) in dry toluene (30 mL) was added a 1 M solution of DIBALH (20 mL) in toluene dropwise using a syringe over a period of 30 min under argon, and the resulting solution was stirred at −78 °C for 3 h. After the completion of the reaction (TLC), amine (20 mmol) was added in one portion, and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The argon balloon was then removed, and the reaction mixture was stirred under air for 8 h, the precipitate formed was filtered off, and the filtrate was concentrated to get diimines **2** (89%), **3** (98%), and **4** (86%) which were used as such without further purification.

General Procedure for the Preparation of β-Lactams 7a-f and 8g. A solution of acid chloride **5-6** (6 mmol) in anhydrous methylene chloride (40 mL) was added to a solution of diimine **2-4** (2 mmol) and triethylamine (18 mmol) in methylene chloride (30 mL) at −23 °C under argon. The resulting mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was then successively washed with water (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the crude product, which was then column chromatographed (silica gel, petroleum ether/acetone mixtures) to give pure β-lactams **7** and **8g** in 52-73% yield. Representative spectroscopic and analytical data for compound **7a** follow.[9]

(4*S*,5*S*,3′*R*,4′*S*)-2,2-Dimethyl-4,5-bis(1′-benzyl-2′-oxo-3′-phenoxyazetidin-4′-yl)-1,3-dioxolane (7a). White crystalline solid (acetone–petroleum ether). $[\alpha]^{25}_D$: +141.8 (*c* 1, CH_2Cl_2).

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(9) Spectroscopic and analytical data of compounds not included in the Experimental Section are described in the supplementary material.

^{1}H-NMR: δ 1.45 (s, 6 H); 3.90–4.05 (m, 2 H); 4.20–4.30 (m, 2 H); 4.35 (d, J = 16 Hz, 2 H); 4.85 (d, J = 16 Hz, 2 H); 5.10 (d, J = 5 Hz, 2 H); 6.70 (d, J = 9 Hz, 4 H); 6.85–7.00 (m, 2 H); 7.10–7.25 (m, 4 H); 7.30–7.55 (m, 10 H). ^{13}C-NMR: δ 27.2, 45.9, 57.4, 79.1, 79.6, 109.7, 114.8, 122.3, 128.0, 128.9, 129.8, 135.9, 156.6, 165.8. IR ($CHCl_3$): ν 1760, 1600, and 1470 cm^{-1}. Anal. Calcd for $C_{37}H_{36}O_6N_2$: C, 73.48; H, 6.00; N, 4.63. Found: C, 73.40; H, 6.12; N, 4.58.

Preparation of β-Lactams 7d and 8d. A solution of the acid chloride (6 mmol) in anhydrous methylene chloride (40 mL) was added to a solution of the diimine **3** (2 mmol) and triethylamine (18 mmol) in methylene chloride (30 mL) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and stirred for 14 h. After the usual workup and flash column chromatography [silica gel (230–400 mesh), petroleum ether/EtOAc (85/15)] pure β-lactams **7d** (56%) and **8d** (25%) were obtained in 81% total yield. Spectroscopic and analytical data for compound **8d** follows.

(4*S*,5*S*,3′*R*,4′*S*,3″*S*,4″*R*)-2,2-Dimethyl-4,5-bis[1′-(*p*-methoxyphenyl)-3′-(benzyloxy)-2′-oxo-azetidin-4′-yl]-1,3-dioxolane (8d). $[\alpha]^{25}_D$: +9.9 (*c* 1, CH_2Cl_2). ^{1}H-NMR: δ 1.15 (s, 3 H); 1.40 (s, 3 H); 3.75 (s, 3 H); 3.80 (s, 3 H); 4.40–4.50 (m, 2 H); 4.50–4.70 (m, 5 H); 4.75–4.95 (m, 3 H); 6.80–6.90 (m, 4 H); 7.25–7.50 (m, 14 H). ^{13}C-NMR: δ 27.0, 27.3, 55.5, 57.8, 58.4, 73.0, 73.7, 75.6, 76.0, 79.9, 80.8, 110.0, 114.1, 114.5, 119.4, 120.5, 121.6, 128.2, 128.4, 128.5, 128.6, 130.6, 130.9, 136.6, 136.7, 156.7, 156.8, 165.1. IR ($CHCl_3$): ν 1740 and 1510 cm^{-1}. MS: m/z 664 (M^+). Anal. Calcd for $C_{39}H_{40}O_8N_2$: C, 70.46; H, 6.06; N, 4.21. Found: C, 70.65; H, 6.18; N, 4.24.

General Procedure for the Preparation of Diols 11a–d, 9d, and 9g by the Deprotection of the Isopropylidene Moiety. To a solution of protected β-lactam **7** or **8** (1 mmol) in THF (10 mL) was added a 2.5 M aqueous solution of perchloric acid (6 mL), and the reaction mixture was stirred at room temperature for 4–8 h. After the completion of the reaction (TLC), the reaction mixture was neutralized by slow addition of solid $NaHCO_3$ and then diluted with water (10 mL) and extracted with methylene chloride (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to get the deprotected diol which was then column chromatographed (silica gel, chloroform/ethyl acetate mixtures) to get pure diols **11a–d** and **9d,g** in almost quantitative yields. Representative spectroscopic and analytical data for compounds **11a** and **9d** follow.[9]

(1*S*,2*S*,3′*R*,4′*S*)-1,2-Bis(1′-benzyl-2′-oxo-3′-phenoxyazetidin-4′-yl)ethane-1,2-diol (11a). Reaction time: 7 h. White crystalline solid (CCl_4). $[\alpha]^{25}_D$: +151.9 (*c* 1, CH_2Cl_2). ^{1}H-NMR: δ 2.50 (s, 1 H); 2.55 (s, 1 H); 3.90 (dd, J = 2, 6 Hz, 2 H); 4.10 (dd, J = 2, 5.3 Hz, 2 H); 4.45 (d, J = 15.5 Hz, 2 H); 4.80 (d, J = 15.5 Hz, 2 H); 5.20 (d, J = 5.3 Hz, 2 H); 7.00–7.15 (m, 6 H); 7.20–7.50 (m, 14 H). ^{13}C-NMR: δ 45.8, 59.3, 71.1, 80.6, 116.1, 112.9, 128.0, 128.6, 129.0, 136.0, 157.5, 166.8. IR ($CHCl_3$): ν 3550 (bs), 1760, and 1600 cm^{-1}. Anal. Calcd for $C_{34}H_{32}O_6N_2$: C, 72.30; H, 5.71; N, 4.90. Found: C, 71.84; H, 5.67; N, 4.83.

(1*S*,2*S*,3′*R*,4′*S*,3″*S*,4″*R*)-1,2-Bis[1′-(*p*-methoxyphenyl)-3′-(benzyloxy)-2′-oxo-azetidin-4′-yl)ethane-1,2-diol (9d). Reaction time: 8 h. White solid (EtOH). $[\alpha]^{25}_D$: +31.6 (*c* 1, CH_2Cl_2). ^{1}H-NMR: δ 2.85 (bs, 1 H); 3.15 (bs, 1 H); 3.75 (s, 3 H); 3.80 (s, 3 H); 4.15 (d, J = 6 Hz, 1 H); 4.25–4.45 (m, 2 H); 4.55 (m, 1 H); 4.60–5.10 (m, 6 H); 6.70 (d, J = 9 Hz, 2 H); 6.85 (d, J = 9 Hz, 2 H); 7.17 (d, J = 9 Hz, 2 H); 7.25–7.45 (m, 10 H); 7.50 (d, J = 9 Hz, 2 H). IR ($CHCl_3$): ν 3500 (bs), 1750, and 1520 cm^{-1}. MS: m/z 624 (M^+). Anal. Calcd for $C_{36}H_{36}O_8N_2$: C, 69.21; H, 5.80; N, 4.48. Found: C, 69.32; H, 5.68; N, 4.63.

General Procedure for the Oxidative Cleavage of Diols 11a–d, 9d, and 9g. To a solution of diol **9** or **11** (1 mmol) in methanol or acetone (15 mL) and water (3 mL) was added powdered $NaIO_4$ (3 mmol) at room temperature, and the reaction mixture was stirred for 4–12 h. As the reaction progressed a white solid precipitated. After the completion of the reaction (TLC), the reaction mixture was filtered, the residue was washed with methanol, and the combined filtrates were concentrated on a rotary evaporator. The residue was treated with water and extracted with methylene chloride (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated to get the 4-formyl β-lactam, which was then filtered through a column (silica gel, acetone/petroleum ether (1:4)) to get pure aldehydes **12a–d**, **10d**, and **10g** in quantitative yields. Representative spectroscopic and analytical data for compound **12a** follow.[9]

(3*R*,4*R*)-*N*-Benzyl-3-phenoxy-4-formylazetidin-2-one (12a). Reaction time: 4 h (in methanol). $[\alpha]^{25}_D$: +57.6 (*c* 0.75, CH_2Cl_2). ^{1}H-NMR: δ 4.25 (dd, J = 2.9, 5 Hz, 1 H); 4.50 (d, J = 11.7 Hz, 2 H); 4.75 (d, J = 11.7 Hz, 1 H); 5.45 (d, J = 5 Hz, 1 H); 7.00–7.15 (m, 3 H); 7.25–7.45 (m, 7 H); 9.50 (d, J = 2.9 Hz, 1 H). ^{13}C-NMR: δ 46.2, 63.3, 82.4, 115.7, 123.1, 128.6, 128.9, 129.3, 129.9, 134.3, 157.1, 164.6, 197.2. IR ($CHCl_3$): ν 1750, 1715, and 1600 cm^{-1}. MS: m/z 281 (M^+). Anal. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.97. Found: C, 72.65; H, 5.43; N, 4.86.

(3*R*,4*R*)-*N*-Benzyl-3-(benzyloxy)-4-formylazetidin-2-one (12b). Reaction time: 8 h (in methanol). White crystalline solid (CCl_4–petroleum ether). $[\alpha]^{25}_D$: +86.2 (*c* 1, CH_2Cl_2) [lit.[3c] for the antipode mp 112–113 °C (EtOAc); $[\alpha]^{25}_D$ = −85.9 (*c* 1, CH_2Cl_2)]. Other spectroscopic and analytical data were identical with the reported[3c] values.

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Supplementary Material Available: Spectroscopic and analytical data for **7b–f**, **8g**, **9g**, **10d**, **10g**, **11b–d**, and **12c–d** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.