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Asymmetric synthesis of β-lactams by [2+2] cycloaddition using 1,4:3,6-dianhydro-D-glucitol (isosorbide) derived chiral pools

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Abstract—Highly diastereoselective synthesis of *cis*-β-lactams via [2+2] cycloaddition reactions of imines derived from a chiral bicyclic aldehyde and ketenes is described. The chiral bicyclic aldehyde as well as chiral acids were prepared from commercially available inexpensive isosorbide. The cycloaddition reaction was found to be highly diastereoselective; in some cases giving a single diastereomer of *cis*-azetidin-2-one in very good yields. A moderate diastereoselectivity was observed with chiral ketenes derived from isosorbide.

1. Introduction

The β-lactam skeleton is the key structural unit responsible for the antibacterial property of the most widely employed antibacterial agents.[1] The resistance developed by the microorganisms against the most traditional β-lactam antibiotic drugs, maintained the interest of organic chemists for the development of new β-lactam drugs displaying broader antibacterial activity.[2] As a consequence, a large number of synthetic methods for β-lactams are now available, and the topic has been reviewed on more than one occasion.[3] The most convenient procedure for the synthesis of the β-lactam ring skeleton is the [2+2] cyclocondensation of ketenes to the imines, known as the Staudinger reaction.[4] In particular, this method has provided useful and economical entries to β-lactams, mainly due to the ready availability of both Schiff's bases and ketenes. In this context, in spite of the high level of achievement reached in the Staudinger reaction, the subject still continues to be an active area of research.[5] Over the past few years, asymmetric versions of this reaction has been extensively developed using a combination of either chiral ketenes and achiral imines or achiral ketenes and chiral imines, generally providing good diastereoselectivity.[6]

In the diastereoselective synthesis of β-lactams, chiral starting materials such as aldehydes, acids/acid halides and amines have been widely used. High levels of stereoselection were achieved when the β-carbon of the chiral aldehyde is attached to a hetero-atom.[7] In recent years, several researchers have studied different approaches to optically pure β-lactams of predictable absolute stereochemistry.[8,9] It has been shown that the reaction of an acid chloride (or equivalent) with a Schiff's base derived from an optically active aldehyde and an achiral amine, in the presence of triethylamine leads to a very high level of diastereoselectivity. In some cases, a single, optically pure, *cis*-β-lactam is obtained.[10d,e,f]

2. Results and discussion

We have been studying the Staudinger reaction for the diastereoselective construction of the β-lactam ring for several years.[10] In this publication we wish to report our work on the application of isosorbide derived optically pure (3a*R*,4*S*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]-dioxole-4-carbaldehyde, a bicyclic aldehyde (**5**) (Scheme 1), 2-((3*R*,3a*R*,6*S*,6a*R*)-6-acetoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)acetic acid (**14**) (Scheme 3) and 2-((3*S*,3a*R*, 6*R*,6a*R*)-6-methoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)acetic acid, bicyclic acid (**21**) (Scheme 5) for the synthesis of variously substituted chiral *cis*-β-lactams via the Staudinger reaction.

Isosorbide is commercially available in large quantities as a by-product from the starch industry and it is obtained by dehydration of D-sorbitol.[11] Apart from its nitro derivatives being used in medicine as vasodilators,[12] benzamidines as factor Xa inhibitors,[13] and in spite of its commercial availability, it has not been fully exploited in the asymmetric

Keywords: Asymmetric synthesis; Staudinger reaction; Ketenes; Imines; Azetidinones.
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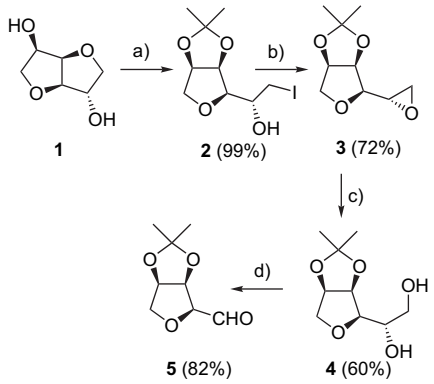


Scheme 1. Reagents and conditions: (a) TMSCl, NaI, acetone, rt, 12 h; (b) NaH, THF, rt, 5 h; (c) NaOH, THF reflux, 48 h; (d) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 6 h.

organic syntheses. However, there are some sporadic instances, where it has been transformed to a chiral phase transfer catalyst,[14] chiral aminoalcohols,[15] and also used as a chiral auxiliary.[16]

As a part of our ongoing research programme on the application of commercially available inexpensive chiral materials for asymmetric synthesis of β-lactams [10a,c,d,f,17] we have used isosorbide as a chiral source for the synthesis of β-lactams. Isosorbide was stereoselectively transformed to an iodoalcohol **2** by a known procedure,[18] which was further converted to epoxide **3** by treating with sodium hydride in THF at 0 °C. The epoxide **3** on reaction with aqueous sodium hydroxide in refluxing THF gave diol **4** as a white crystalline solid. Our attempt to convert iodoalcohol **2** to diol **4** directly by the treatment with aqueous sodium hydroxide was unsuccessful. The diol **4** on oxidative cleavage with sodium metaperiodate gave (3a*R*,4*S*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (**5**), a chiral bicyclic aldehyde, in very good overall yield. We envisaged that the Schiff's base derived from **5** would give a good diastereoselectivity in the cycloaddition reaction with ketene as it has a hetero-atom on the β-carbon atom and also the rigid cis-fused bicyclic ring structure would provide very good facial selectivity. This is clear from the molecular structure shown in Figure 1.[19] In fact the Schiff's base derived from this bicyclic aldehyde **5** on reaction with ketene derived from methoxyacetyl chloride and triethylamine, gave exclusively a single diastereomer of *cis*-β-lactam (**9a**) (Scheme 2). No trace of the other diastereomer was detected either in the ^{1}H NMR spectrum or from HPLC analysis of the crude reaction product.[20] The cis stereochemistry of the β-lactam ring was ascertained from the coupling constant of the β-lactam ring protons (J=5.4 Hz for cis-isomer). The absolute stereochemistry of the newly formed chiral centres was established as 3*S*, 4*R* from the single crystal X-ray analyses[21,22] of the β-lactam **9a** (Fig. 2), which was obtained by recrystallization from ethyl acetate/petroleum ether as colourless cubes. The generality of this reaction was established by preparing large number of β-lactams in very good yields and excellent optical purities (Table 1).

After establishing the excellent diastereoselectivity in the cycloaddition reaction of imines derived from isosorbide and ketenes we were also interested to know the

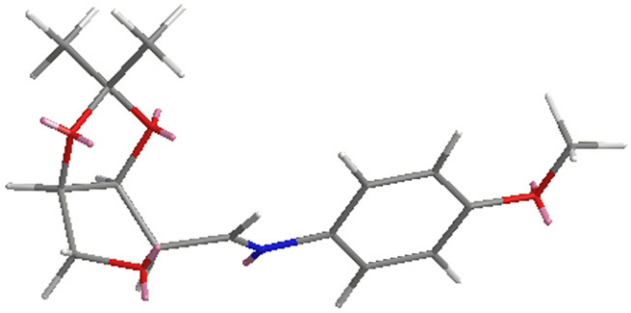
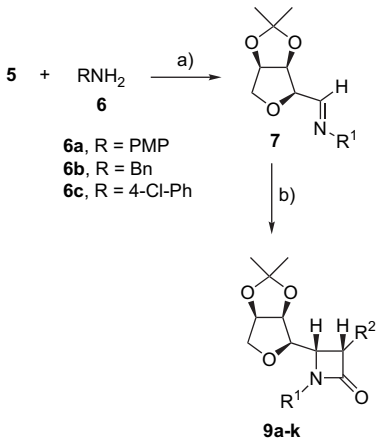


Figure 1. Molecular model of Schiff's base **7a**.



Scheme 2. Reagents and conditions: (a) $MgSO_4$, CH_2Cl_2, rt, 15 h; (b) R^2OCH_2COCl (**8**), Et_3N, CH_2Cl_2, 0 °C to rt, 15 h.

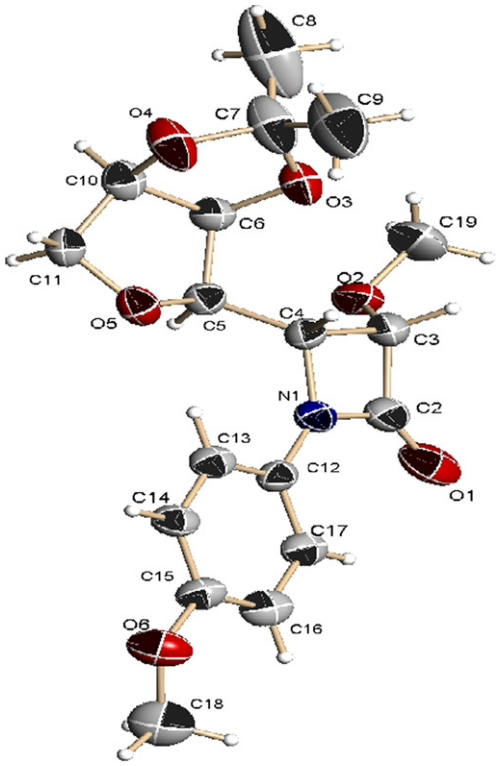
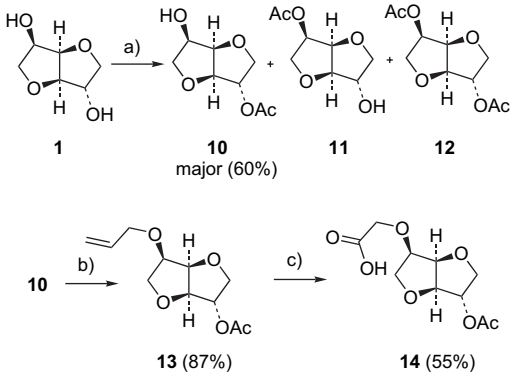


Figure 2. ORTEP diagram for compound **9a**.

Table 1. Synthesis of azetidin-2-ones (**9a–k**)

Entry no.	Compd	R^1	R^2	HPLC[b] purity	Yield[c] (%)
1	**9a**	PMP[a]	OCH_3	98	74
2	**9b**	PMP	OBn	99	78
3	**9c**	PMP	OPh	97	75
4	**9d**	PMP	OAc	97	75
5	**9e**	CH_2Ph	OCH_3	95	67
6	**9f**	CH_2Ph	OBn	96	70
7	**9g**	CH_2Ph	OPh	96	60
8	**9h**	CH_2Ph	OAc	96	61
9	**9i**	4-Cl-Ph	OCH_3	98	68
10	**9j**	4-Cl-Ph	OBn	98	71
11	**9k**	4-Cl-Ph	OPh	97	62

[a] PMP=*p*-methoxyphenyl.
[b] Purity was determined by HPLC analysis on Chromsphere Chromsep 5 C-18, 250×4.6 mm (5 μm) column; solvent system (v/v): MeCN/H_2O (60:40), flow rate 1.5 mL/min.
[c] Isolated yields.



Scheme 3. Reagents and conditions: (a) AcOH, CH_2Cl_2/DMAP/DCC, rt, 3 h; (b) allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark rt; (c) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, 0 °C, 6 h.

diastereoselectivity in the cycloaddition reaction of chiral ketenes derived from isosorbide and achiral imines. It has been shown that the two hydroxyl groups present in isosorbide have different reactivities as they are sterically and electronically different. The C-5 *endo*-hydroxyl group is involved in intramolecular H-bonding while the other C-2 *exo*-hydroxyl group is free (Fig. 3).[23] One can selectively acylate the C-2 hydroxyl groups.[24] We have exploited this reactivity difference and prepared two chiral acetic acid derivatives from isosorbide and used them as ketene precursors in the synthesis of β-lactams using Staudinger cycloaddition reaction with various imines.

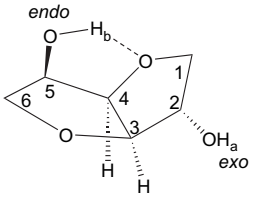


Figure 3. Structure of isosorbide **1**.

The acylation of isosorbide with acetic acid using DCC gave a mixture monoacetates **10**, **11** and diacetate **12** of which the pure major monoacetate **10** (60%) was separated by column chromatography. All our efforts to alkylate C-5 *endo*-hydroxyl with ethylbromoacetate using sodium hydride under various reaction conditions were unsuccessful. Therefore, it was reacted with allyl bromide in the presence of silver oxide and calcium sulfate to get the *O*-allyl-monoacetate-isosorbide **13** in very good yield. The *O*-allyl-monoacetate **13** was further oxidized with catalytic $RuCl_3$ and $NaIO_4$ as secondary oxidant in $CH_3CN/CCl_4/H_2O$ (2:2:3)[25] for 12 h at 0 °C to furnish the desired chiral bicyclic acid **14** in 53% yield (Scheme 3). The Staudinger reaction of this *endo*-chiral bicyclic acid **14** with imine **15a** in the presence of Et_3N, triphosgene as an acid activator[26] in dichloromethane at 0 °C to room temperature for 15 h gave a diastereomeric mixture of β-lactams **16a** and **17a** (~80:20, from ^1H NMR of the crude product) (Scheme 4). All our efforts to purify the major diastereomer by flash column were unsuccessful. However, the major diastereomer **16a** was obtained in pure form as a white crystalline solid by crystallization from methanol. The cis stereochemistry of the β-lactam ring was ascertained from the coupling constant of the ring protons (J=5.4 Hz for cis-isomer). The absolute stereochemistry of the newly formed chiral centres was further established as 3*R*, 4*S* from the single crystal X-ray analyses[27] of **16a** (Fig. 4).

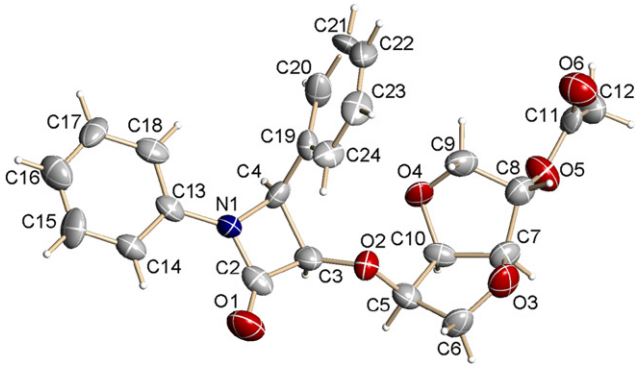
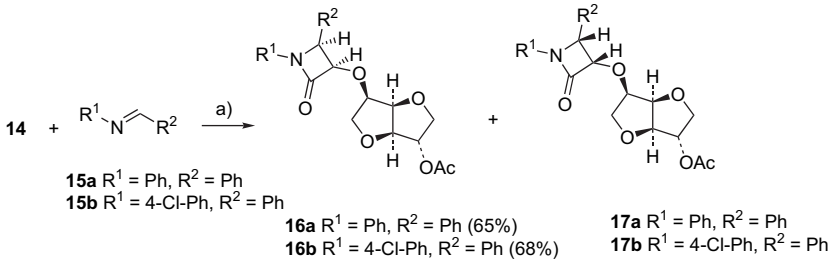
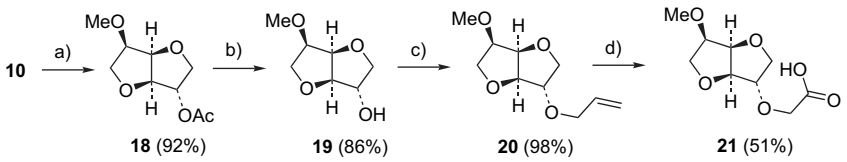


Figure 4. ORTEP diagram for compound **16a**.

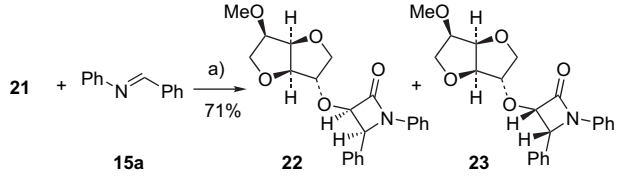


Scheme 4. Reagents and conditions: (a) triphosgene, Et_3N, DCM, 0 °C to rt, 15 h.



Scheme 5. Reagents and conditions: (a) CH_3I, Ag_2O, $CaSO_4$, 2 days, dark rt; (b) KOH, EtOH, 30 min, 50 °C; (c) allyl bromide, Ag_2O, $CaSO_4$, 2 days, dark rt; (d) $KMnO_4$, K_2CO_3, acetone, rt, 3 h.

As there was moderate selectivity in the cycloaddition reaction of ketenes derived from *endo*-acid **14**, we also wanted to examine the selectivity with acid **21** possessing an *exo*-acetic acid side chain on C-2 oxygen of the isosorbide. This *exo*-acid **21** can be easily prepared by a synthetic manipulation as shown in Scheme 5. The monoacetate **10** was methylated using methyl iodide and Ag_2O in the presence of calcium sulfate to get methoxyacetate **18** in 92% yield. This methoxyacetate **18** was further hydrolysed with ethanolic potassium hydroxide to give methoxy-alcohol **19**, which was alkylated with allyl bromide under similar reaction conditions used in the synthesis of **13** to get an allyl ether **20** in excellent yield. It was oxidized with $KMnO_4$ in acetone in the presence of K_2CO_3 to get chiral bicyclic *exo*-acid **21** in 51% yield. The asymmetric Staudinger reaction of chiral bicyclic acid **21** with achiral imine **15a** afforded an inseparable diastereomeric mixture of two *cis*-β-lactams **22** and **23** (Scheme 6). In this case there was no diastereoselectivity in the β-lactam formation (~50:50 from ^{1}H NMR of the crude product). All our attempts to separate these isomers either by flash column chromatography or recrystallization were unsuccessful. A low diastereoselectivity in the β-lactam formation in case of *exo*-ketene was expected, as there is no facial differentiation in the transition state during the ketene–imine cycloaddition reaction. However, in case of *endo*-ketene generated from acid **14**, the rigid bicyclic framework of the isosorbide has considerable effect on the diastereoselectivity in the cycloaddition reaction with imine.



Scheme 6. Reagents and conditions: (a) triphosgene, Et_3N, DCM, 0 °C to rt, 15 h.

3. Conclusion

In conclusion, we have synthesized bicyclic chiral aldehyde from isosorbide and the imines derived from this aldehyde were used in the synthesis of azetidin-2-ones via [2+2] cycloaddition reaction with ketenes. The reaction was highly stereoselective and in most of the cases a single diastereomer was obtained in very good yields. The *endo*-chiral ketene derived from isosorbide also showed diastereoselectivity in the Staudinger cycloaddition reaction. However, no selectivity was observed when *exo*-chiral ketene was used in the cycloaddition reaction.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV 200 or AV 400 spectrometers and chemical shifts are reported in parts per million downfield from tetramethylsilane for ^{1}H NMR. Infrared spectra were recorded on Perkin–Elmer infrared spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. MS analyses were performed on a Peseiex API QSTAR Pulsar with an electrospray ionization mass spectrometer (LC-MS), using MeOH as a solvent (*m*/*z*, fragmentor 70 V). The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108 elemental analyzer. Optical rotations were recorded on an ADP-200 polarimeter under standard conditions. HPLC: HP-1050 Ti series pump, JASCO 970 detector, at 254 nm connected to HP 3396 series-II integrator; column: Chromsphere Chromsep 5 C-18, 250×4.6 mm (5 μm); solvent system (v/v): MeCN/H_2O (60:40), flow rate 1.5 mL/min.

4.1.1. (*S*)-1-((3a*R*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethane-1,2-diol (4). To the solution of epoxide **3** (0.5 g, 2.66 mmol) in a mixture of THF (10 mL) and water (5 mL) was added aqueous NaOH (1 M, 3.5 mL) and refluxed for 48 h. The THF was then removed under reduced pressure and the aqueous layer acidified dropwise with dilute HCl (pH=2) and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give diol **4** as a white solid (0.330 g, 60%); mp 89–90 °C [Found: C, 52.84; H, 7.82. $C_9H_{16}O_5$ requires C, 52.93; H, 7.89%]; $[\alpha]_D^{26}$ −40.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3433, 1382, 1215 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.32 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 2.45 (2H, br s, O*H*), 3.47–3.54 (2H, m, C*H*$_2$OH), 3.79 (2H, t, *J* 3.6 Hz, CHC*H*$_2$O), 4.06–4.13 (2H, m, OC*H*C*H*OH), 4.72 (1H, dd, *J* 6.2, 3.6 Hz, OC*H*CH), 4.81 (1H, dd, *J* 6.2, 3.6 Hz, OC*H*CH$_2$O); δ_C (50 MHz, $CDCl_3$) 24.4, 25.8, 63.5, 70.7, 72.6, 80.6, 81.3, 82.2, 112.4; MS: *m*/*z* 204 (M^+).

4.1.2. (3a*R*,4*S*,6a*R*)-2,2-Dimethyl-tetrahyrdofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (5). To a vigorously stirred suspension of chromatographic grade silica (3.3 g) in dichloromethane (15 mL) in a 100 mL flask was added aqueous solution (0.65 M) of $NaIO_4$ (3.5 mL) dropwise with stirring. Diol **4** (0.330 g, 1.61 mmol) in dichloromethane (15 mL) was then added dropwise and the reaction was stirred at room temperature. The reaction was stirred until the disappearance of the starting material (5 h, by TLC).

The reaction mixture was filtered and the filtrate was washed with water (10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to afford pure bicyclic aldehyde **5** as oil (0.228 g, 82%); $[\alpha]_D^{26}$ −97.1 (*c* 0.2, $CHCl_3$) [Found: C, 55.73; H, 6.96. $C_8H_{12}O_4$ requires C, 55.80; H, 7.02%]; ν_{max} ($CHCl_3$) 1215, 1350, 1737 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 3.63 (1H, dd, *J* 10.7, 3.6 Hz, CH$_a$*H*$_b$OH), 3.97 (1H, d, *J* 4.8 Hz, C*H*$_a$H$_b$OH), 4.23 (1H, d, *J* 10.7 Hz, OC*H*CH$_2$O), 4.86 (1H, dd, *J* 5.9, 3.6 Hz, OC*H*CH), 5.03 (1H, dd, *J* 5.9, 4.8 Hz, C*H*CHO), 9.67 (1H, d, *J* 1.3 Hz, C*H*O); δ_C (50 MHz, $CDCl_3$) 24.5, 25.8, 73.3, 80.7, 81.8, 85.9, 113.2, 198.4; MS: *m*/*z* 172 (M^+).

4.1.3. (*E*)-*N*-(((3a*S*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene)-4-methoxybenzenamine (6a). To a solution of aldehdye **5** (0.210 g, 1.22 mmol) in dichloromethane (20 mL) and anhydrous $MgSO_4$ (0.307 g, 2.44 mmol) was added *p*-anisidine (0.165 g, 1.34 mmol) in dichloromethane (10 mL) at room temperature and the mixture stirred for 15 h. Then the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give imine **6a** (0.320 g, 94%) as brown oil; ν_{max} ($CHCl_3$) 1689, 1600, 1500, 1244 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.41 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 3.75–3.83 (5H, m, CHC*H*$_2$O and OC*H*$_3$), 4.43–4.91 (3H, m, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 6.85–7.06 (2H, m, Ar-*H*), 7.43–7.48 (2H, m, Ar-*H*), 8.34 (1H, d, *J* 1.6 Hz, OCHCHC*H*=N).

4.1.4. (*E*)-*N*-(((3a*S*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene) (phenyl methanamine) (6b). Yield 95%; pale yellow oil; ν_{max} ($CHCl_3$) 1683, 1558, 1456, 1217 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 3.51 (1H, dd, *J* 10.8, 3.2 Hz, CHC*H*$_a$H$_b$O), 3.82 (2H, s, C*H*$_2$Ph); 3.96–4.11 (1H, m, CHCH$_a$*H*$_b$O), 4.55–4.85 (3H, m, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 7.15–7.30 (5H, m, Ar-*H*), 7.89 (1H, d, *J* 1.6 Hz, OCHCHC*H*=N).

4.1.5. (*E*)-4-Chloro-*N*-(((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methylene)benzenamine (6c). Yield 96%; yellow oil; ν_{max} ($CHCl_3$) 1681, 1600, 1495, 1269 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (3H, s, C*H*$_3$), 1.54 (3H, s, C*H*$_3$), 3.31–4.95 (5H, m, CHC*H*$_2$O, OC*H*CH$_2$, OC*H*CHCH=N, OCHC*H*CH=N), 6.53–6.68 (2H, m, Ar-*H*), 7.09–7.33 (2H, m, Ar-*H*), 8.35 (1H, d, *J* 1.6 Hz, OCHCHC*H*=N).

The imines **6a–c** were used without purification for the next step.

4.1.6. Typical procedure for the synthesis of (3*S*,4*R*)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (9a). A solution of the methoxyacetyl chloride (0.188 g, 1.73 mmol) in dichloromethane (10 mL) was added to a cooled solution of imine **6a** (0.320 g, 1.15 mmol) and triethylamine (0.350 g, 3.46 mmol) in anhydrous dichloromethane (15 mL) at 0 °C. It was then allowed to warm to room temperature and stirred for 15 h. The reaction mixture was then diluted with dichloromethane (10 mL) and washed successively with water (2×10 mL), satd $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product on purification by flash column chromatography using 20% ethyl acetate/petroleum ether as an eluent gave a single diastereomer, *cis*-β-lactam **9a** as white crystalline solid (0.300 g, 74%); mp 155–156 °C [Found: C, 61.70; H, 6.57; N, 4.00. $C_{18}H_{23}NO_6$ requires C, 61.86; H, 6.64; N, 4.01%]; R_f (20% ethyl acetate/petroleum ether) 0.52; $[\alpha]_D^{26}$ −138.8 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.36 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$), 3.43 (1H, dd, *J* 10.9, 3.7 Hz, C*H*$_a$H$_b$OCH), 3.68 (3H, s, OC*H*$_3$), 3.70 (1H, dd, *J* 7.5, 3.7 Hz, CH$_a$*H*$_b$OCH), 3.79 (3H, s, PhOC*H*$_3$), 4.09 (1H, d, *J* 10.9 Hz, OCHC*H*), 4.52 (1H, dd, *J* 8.7, 5.4 Hz, C$_4$*H*), 4.69 (1H, d, *J* 5.4 Hz, C$_3$*H*), 4.78 (1H, dd, *J* 6.1, 3.7 Hz, OC*H*CH$_2$), 4.91 (1H, dd, *J* 6.1, 3.7 Hz, OC*H*CH), 6.85 (2H, d, *J* 9.8 Hz, Ar-*H*), 7.64 (2H, d, *J* 9.8 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.7, 26.1, 55.4, 58.9, 59.8, 72.7, 80.8, 82.7, 83.1, 112.2, 113.9, 119.5, 131.3, 156.4, 165; MS: *m*/*z* 349 (M^+).

Following the similar procedure other *cis*-β-lactam **9b–k** were synthesized.

4.1.7. (3*S*,4*R*)-3-(Benzyloxy)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(-4-methoxyphenyl)azetidin-2-one (9b). It was purified by flash column chromatography (20% ethyl acetate/petroleum ether); yield 78%; colourless oil [Found: C, 67.53; H, 6.28; N, 3.12. $C_{24}H_{27}NO_6$ requires C, 67.74; H, 6.40; N, 3.29%]; R_f (20% ethyl acetate/petroleum ether) 0.47; $[\alpha]_D^{26}$ −118.1 (*c* 1, $CHCl_3$); ν_{max} (neat) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.39 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 3.41 (1H, dd, *J* 10, 3.3 Hz, C*H*$_a$H$_b$OCH), 3.71–3.77 (1H, m, CH$_a$*H*$_b$OCH), 3.79 (3H, s, PhOC*H*$_3$), 4.12 (1H, d, *J* 11.5 Hz, OC*H*$_a$H$_b$Ph), 4.55 (1H, d, *J* 5.4 Hz, C$_4$*H*), 4.75 (1H, dd, *J* 5.4, 4.4 Hz, C$_3$*H*), 4.85 (1H, d, *J* 11.5 Hz, OCH$_a$*H*$_b$Ph), 4.92–5.04 (3H, m, OC*H*CH$_2$, OC*H*CH, OCHC*H*), 6.86 (2H, d, *J* 8.8 Hz, Ar-*H*), 7.35–7.41 (5H, m, Ar-*H*), 7.67 (2H, d, *J* 8.8 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.6, 26.0, 55.3, 59.0, 72.5, 73.6, 80.7, 83.0, 112.0, 113.8, 119.4, 127.7, 127.9, 128.4, 131.3, 137.2, 156.3, 165; MS: *m*/*z* 425 (M^+).

4.1.8. (3*S*,4*R*)-4-((3a*S*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (9c). It was purified by flash column chromatography (15% ethyl acetate/petroleum ether); yield 75%; white solid; mp 177–178 °C [Found: C, 67.09; H, 6.08; N, 3.28. $C_{23}H_{25}NO_6$ requires C, 67.13; H, 6.13; N, 3.41%]; R_f (15% ethyl acetate/petroleum ether) 0.66; $[\alpha]_D^{26}$ −224.3 (*c* 1.2, $CHCl_3$); ν_{max} (nujol) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.29 (3H, s, C*H*$_3$), 1.56 (3H, s, C*H*$_3$), 3.49 (1H, dd, *J* 10, 3.5 Hz, C*H*$_a$H$_b$OCH), 3.81 (3H, s, PhOC*H*$_3$), 3.91 (1H, dd, *J* 8.7, 3.5 Hz, CH$_a$*H*$_b$OCH), 4.12 (1H, d, *J* 10.8 Hz, OCHC*H*), 4.71–4.82 (2H, m, OC*H*CH$_2$, OC*H*CH), 4.95 (1H, dd, *J* 5.4, 3.6 Hz, C$_4$*H*), 4.46 (1H, d, *J* 5.4 Hz, C$_3$*H*), 6.88 (2H, d, *J* 8.6 Hz, Ar-*H*), 7.35–7.41 (5H, m, Ar-*H*), 7.72 (2H, d, *J* 8.6 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.3, 26.0, 55.3, 58.7, 72.8, 80.0, 80.7, 82.8, 112.0, 113.8, 116.2, 119.5, 122.5, 129.4, 131.1, 156.4, 157.8, 163.4; MS: *m*/*z* 411 (M^+).

4.1.9. (2*R*,3*S*)-2-((3a*S*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (9d). It was purified by flash column chromatography (20% ethyl acetate/petroleum ether); yield 75%; thick oil [Found: C, 60.38; H, 6.08; N, 3.65. $C_{19}H_{23}NO_7$ requires C, 60.47; H, 6.14; N, 3.71%]; R_f (20% ethyl acetate/petroleum ether) 0.38; $[\alpha]_D^{26}$ −134.1 (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$) 1750 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.19 (3H, s, CH_3COO), 3.5 (1H, dd, *J* 11, 3 Hz, CH_aH$_b$OCH), 3.44–3.79 (1H, m, CH$_a$$H_b$OCH and 3H, s, PhOC$H_3$), 4.31 (1H, d, *J* 10.8 Hz, OCHC*H*), 4.59–4.63 (1H, m, OC*H*CH$_2$), 4.72–4.89 (2H, m, OC*H*CH and C_4H), 6.24 (1H, d, *J* 5.4 Hz, C_3H), 6.85 (2H, d, *J* 8.8 Hz, Ar-*H*), 7.65 (2H, d, *J* 8.8 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 20.6, 24.4, 25.9, 55.3, 58.9, 72.3, 72.7, 80.6, 82.8, 112.5, 113.9, 119.5, 130.9, 156.6, 162.3, 168.3; MS: *m*/*z* 377 (M^+).

4.1.10. (3*S*,4*R*)-1-Benzyl-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-methoxyazetidin-2-one (9e). It was purified by flash column chromatography (10% ethyl acetate/petroleum ether); yield 67%; thick oil [Found: C, 64.72; H, 6.88; N, 4.13. $C_{18}H_{23}NO_5$ requires C, 64.84; H, 6.95; N, 4.20%]; R_f (10% ethyl acetate/petroleum ether) 0.33; $[\alpha]_D^{26}$ −65.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H s, CH_3), 1.39 (3H, s, CH_3), 3.42 (1H, dd, *J* 10.8, 3.4 Hz, CH_aH$_b$OCH), 3.53–3.58 (1H, m, CH$_a$$H_b$OCH), 3.59 (3H, s, OC$H_3$), 3.91 (1H, dd, *J* 8.8, 3.4 Hz, OCHC*H*), 4.04–4.09 (1H, m, OC*H*CH$_2$), 4.25 (1H, d, *J* 14 Hz, NCH_aH$_b$Ph), 4.51 (1H, d, *J* 4.5 Hz, C_3H), 4.70 (1H, d, *J* 14 Hz, NCH$_a$$H_b$Ph), 4.74–4.76 (2H, m, OC*H*CH and C_4H), 5.25–5.31 (5H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.8, 25.9, 45.1, 56.6, 59.4, 72.8, 80.5, 81.0, 83.0, 83.3, 111.3, 127.4, 128.5, 128.8, 167.2; MS: *m*/*z* 333 (M^+).

4.1.11. (3*S*,4*R*)-1-Benzyl-3-(benzyloxy)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)azetidin-2-one (9f). It was purified by flash column chromatography (15% ethyl acetate/petroleum ether); yield 70%; thick oil [Found: C, 70.29; H, 6.54; N, 3.33. $C_{24}H_{27}NO_5$ requires C, 70.38; H, 6.65; N, 3.42%]; R_f (15% ethyl acetate/petroleum ether) 0.32; $[\alpha]_D^{26}$ −58.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, s, CH_3), 1.40 (3H, s, CH_3), 3.43 (1H, dd, *J* 11.7, 3.3 Hz, CH_aH$_b$OCH), 3.65 (1H, dd, *J* 8.3, 3.3 Hz, CH$_a$$H_b$OCH), 3.95 (1H, dd, *J* 8.3, 5.1 Hz, OCHC*H*), 4.09 (1H, d, *J* 10.6 Hz, NCH_aH$_b$Ph), 4.25 (1H, d, *J* 14.6 Hz, OCH_aH$_b$Ph), 4.71–4.77 (5H, m, C_3H, C_4H, OC*H*CH$_2$, OC*H*CH, NCH$_a$$H_b$Ph), 4.92 (1H, d, *J* 11.6 Hz, OCH$_a$$H_b$Ph), 7.26–7.37 (10H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.7, 25.9, 45.1, 56.8, 72.7, 73.1, 80.5, 80.9, 81.3, 83.0, 112.1, 127.4, 127.6, 127.8, 128.2, 128.5, 128.7, 136.0, 137.7, 167.3; MS: *m*/*z* 409 (M^+).

4.1.12. (3*S*,4*R*)-1-Benzyl-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-phenoxyazetidin-2-one (9g). It was purified by flash column chromatography (5% acetone/petroleum ether); yield 60%; thick oil [Found: C, 69.73; H, 6.29; N, 3.44. $C_{23}H_{25}NO_5$ requires C, 69.84; H, 6.38; N, 3.54%]; R_f (5% acetone/petroleum ether) 0.30; $[\alpha]_D^{26}$ −70.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 1758 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (3H, s, CH_3), 1.40 (3H, s, CH_3), 3.48 (1H, dd, *J* 10.8, 3.4 Hz, CH_aH$_b$OCH), 3.78 (1H, dd, *J* 8.8, 3.4 Hz, CH$_a$$H_b$OCH), 4.10–4.19 (2H, m, OCHC*H* and OC*H*CH$_2$), 4.34 (1H, d, *J* 14.5 Hz, NCH_aH$_b$Ph), 4.56–4.58 (1H, m, NCH$_a$$H_b$Ph), 4.71–4.82 (2H, m, C_4H and OC*H*CH), 5.26 (1H, d, *J* 5.5 Hz, C_3H), 6.90–7.39 (10H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.6, 25.9, 30.8, 45.5, 56.5, 73.0, 80.5, 81.0, 82.7, 112.2, 114.6, 116.0, 122.0, 122.2, 127.6, 128.5, 128.8, 137.7, 165.3; MS: *m*/*z* 395 (M^+).

4.1.13. (2*R*,3*S*)-1-Benzyl-2-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-4-oxoazetidin-3-yl acetate (9h). It was purified by flash column chromatography (15% ethyl acetate/petroleum ether); yield 61%; thick oil [Found: C, 63.07; H, 6.26; N, 3.78. $C_{19}H_{23}NO_6$ requires C, 63.15; H, 6.41; N, 3.88%]; R_f (15% ethyl acetate/petroleum ether) 0.33; $[\alpha]_D^{26}$ −37.7 (*c* 1.1, $CHCl_3$); ν_{max} (neat) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.27 (3H, s, CH_3), 1.37 (3H, s, CH_3), 2.14 (3H, s, CH_3COO), 3.48 (1H, dd, *J* 10.7, 3.5 Hz, CH_aH$_b$OCH), 3.69 (1H, dd, *J* 8.8, 3.5 Hz, CH$_a$$H_b$OCH), 4.10 (1H, dd, *J* 8.8, 5.2 Hz, OCHC*H*), 4.25 (1H, d, *J* 14.6 Hz, NCH_aH$_b$Ph), 4.40 (1H, d, *J* 14.6 Hz, NCH$_a$$H_b$Ph), 4.61–4.78 (3H, m, C_4H, OC*H*CH and OC*H*CH$_2$), 5.95 (1H, d, *J* 5.1 Hz, C_3H), 7.27–7.37 (5H, m, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 20.5, 24.5, 25.8, 45.4, 56.1, 72.7, 73.9, 80.3, 81.0, 82.6, 112.6, 127.6, 128.5, 128.7, 164.5, 168.6; MS: *m*/*z* 361 (M^+).

4.1.14. (3*S*,4*R*)-1-(4-Chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-methoxyazetidin-2-one (9i). It was purified by flash column chromatography (10% ethyl acetate/petroleum ether); yield 68%; thick oil [Found: C, 57.68; H, 5.61; N, 3.87; Cl, 9.79. $C_{17}H_{20}NO_5Cl$ requires C, 57.77; H, 5.71; N, 3.97; Cl, 9.90%]; R_f (10% ethyl acetate/petroleum ether) 0.44; $[\alpha]_D^{26}$ −128.0 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 1749 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, s, CH_3), 1.48 (3H, s, CH_3), 3.35 (1H, dd, *J* 10.9, 3.4 Hz, CH_aH$_b$OCH), 3.60 (3H, s, OCH_3), 3.63–3.68 (1H, m, CH$_a$$H_b$OCH), 4.12 (1H, d, *J* 10.9 Hz, OCHC*H*), 4.45 (1H, dd, *J* 8.7, 5.4 Hz, C_4H), 4.62 (1H, d, *J* 5.4 Hz, C_3H), 4.69–4.74 (1H, m, OC*H*CH), 4.80–4.89 (1H, m, OC*H*CH$_2$), 7.18 (2H, d, *J* 8.6 Hz, Ar-*H*), 7.59 (2H, d, *J* 8.6 Hz, Ar-*H*); δ_C (50 MHz, $CDCl_3$) 24.6, 26.1, 59.0, 59.9, 72.7, 80.7, 80.8, 82.8, 83.0, 112.2, 119.4, 128.7, 129.3, 136.3, 165.5; MS: *m*/*z* 353 (M^+).

4.1.15. (3*S*,4*R*)-3-(Benzyloxy)-1-(4-chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)azetidin-2-one (9j). It was purified by flash column chromatography (10% ethyl acetate/petroleum ether); yield 71%; thick oil [Found: C, 64.21; H, 5.73; N, 3.19; Cl, 8.09. $C_{23}H_{24}NO_5Cl$ requires C, 64.32; H, 5.64; N, 3.26; Cl, 8.15%]; R_f (10% ethyl acetate/petroleum ether) 0.28; $[\alpha]_D^{26}$ −117.1 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.33 (1H, dd, *J* 11, 3.4 Hz, CH_aH$_b$OCH), 3.62–3.69 (2H, m, CH$_a$$H_b$OCH, OCHC*H*), 4.01 (1H, d, *J* 9.6 Hz, OCH_aH$_b$Ph), 4.47–4.69 (1H, m, OCH$_a$$H_b$Ph), 4.67–4.72 (1H, m, OC*H*CH), 4.78–4.94 (3H, m, C_3H, C_4H and OC*H*CH$_2$), 7.16–7.58 (7H, m, Ar-*H*), 7.60 (2H, d, *J* 8.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 26.1, 59.2, 72.6, 73.8, 80.7, 80.8, 83.0, 112.1,

119.4, 127.8, 128.0, 128.1, 128.5, 128.7, 129.3, 136.3, 137.0, 165.6; MS: *m*/*z* 429 (M^+).

4.1.16. (3*S*,4*R*)-1-(4-Chlorophenyl)-4-((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-phenoxyazetidin-2-one (9k). It was purified by flash column chromatography (10% ethyl acetate/petroleum ether); yield 62%; thick oil [Found: C, 63.48; H, 5.22; N, 3.29; Cl, 8.45. $C_{22}H_{22}NO_5Cl$ requires C, 63.54; H, 5.33; N, 3.37; Cl, 8.52%]; R_f (10% ethyl acetate/petroleum ether) 0.34; $[\alpha]_D^{26}$ −117.9 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 1764 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 3.43 (1H, dd, *J* 10.0, 3.6 Hz, C*H*$_a$H$_b$OCH), 3.84 (1H, dd, *J* 10.0, 3.6 Hz, CH$_a$*H*$_b$OCH), 4.08 (1H, d, *J* 11.0 Hz, OCHC*H*), 4.69–4.76 (2H, m, OC*H*CH and OC*H*CH$_2$), 4.90 (1H, dd, *J* 5.8, 3.6 Hz, C$_4$*H*), 5.41 (1H, d, *J* 5.8 Hz, C$_3$*H*), 6.77–7.31 (7H, m, Ar-*H*), 7.66 (2H, d, *J* 8.9 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.4, 26.0, 58.9, 72.9, 80.2, 80.7, 80.8, 112.3, 114.6, 115.2, 119.6, 121.8, 122.7, 128.8, 129.6, 136.2, 169.5; MS: *m*/*z* 415 (M^+).

4.1.17. ((3*R*,3a*R*,6*S*,6a*R*)-6-Acetoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)acetic acid (14). To a solution of the 2-*O*-acetyl-5-*O*-allyl-1,4:3,6-dianhydro-D-glucitol **13** (1.0 g, 4.38 mmol) in the mixture of solvent $CH_3CN/CCl_4/H_2O$ (2:2:3, 30 mL), powdered $NaIO_4$ (2.8 g, 13.2 mmol) was added followed by catalytic amount of hydrated $RuCl_3$ (5 mg) at 0 °C. The reaction mixture was stirred for 6 h at this temperature. After completion of the reaction (TLC), the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3×10 mL). The organic layer was washed with saturated $NaHCO_3$ (10 mL) and the alkaline extract was neutralized with dilute HCl (10%) and again extracted with ethyl acetate (3×10 mL). The organic layer was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get pure *endo*-bicyclic acid **14** (0.57 g, 53%) as pale yellow oil [Found: C, 48.78; H, 5.73. $C_{10}H_{14}O_7$ requires C, 48.71; H, 5.64%]; $[\alpha]_D^{26}$ +89.7 (*c* 0.75, $CHCl_3$); ν_{max} ($CHCl_3$) 3300, 1731, 1371, 1238 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.08 (3H, s, COOC*H*$_3$), 3.80–4.29 (7H, m, OCHC*H*$_2$, OC*H*$_2$CH, OC*H*$_2$COOH, OC*H*CH), 4.51 (1H, d, *J* 4.3 Hz, OC*H*CH), 4.75 (1H, t, *J* 4.3 Hz, *H*COCH$_2$COOH), 5.19–5.20 (1H, m, *H*COCH$_2$COOMe), 6.91 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 20.8, 68.1, 70.9, 73.8, 78.1, 80.5, 81.2, 86.0, 170.0, 172.5; MS: *m*/*z* 247 (M^+).

4.1.18. (3*S*,3a*R*,6*R*,6a*R*)-6-((3*R*,4*S*)-2-Oxo-1,4-diphenylazetidin-3-yloxy)hexahydrofuro[3,2-*b*]furan-3-yl acetate (16a). To a stirred solution of the *endo*-bicyclic acid **14** (0.142 g, 0.57 mmol), imine **15a** (0.104 g, 0.57 mmol) and dry triethylamine (0.174 g, 1.73 mmol) in anhydrous dichloromethane (10 mL), a solution of triphosgene (0.085 g, 0.29 mmol) in dichloromethane was added dropswise at 0 °C. The reaction mixture was allowed to come to room temperature and stirred at this temperature for 15 h. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (3×10 mL), saturated bicarbonate solution (3×10 mL) and brine (15 mL), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude product as a brown oil, which was purified by flash column chromatography (30% ethyl acetate/petroleum ether) to get diastereomeric mixture of *cis*-β-lactams **16a** and **17a** (80:20). A major diastereomer of white solid **16a** (0.153 g, 65%) was obtained in pure form by recrystallization of diastereomeric mixture from methanol; mp 72–73 °C [Found: C, 67.47; H, 5.66; N, 3.42. $C_{23}H_{23}NO_6$ requires C, 67.38; H, 5.55; N, 3.35%]; R_f (30% ethyl acetate/petroleum ether) 0.34; $[\alpha]_D^{26}$ +66.0 (*c* 0.20, $CHCl_3$); ν_{max} ($CHCl_3$) 1743, 1735, 1238 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.06 (3H, s, COOC*H*$_3$), 3.13–3.28 (3H, m, OCHC*H*$_2$ and OC*H*CH), 3.74 (1H, dd, *J* 10.5, 5.4 Hz, OC*H*CHAc), 3.95 (2H, br d, *J* 2.8 Hz, OC*H*$_2$CH), 4.33 (1H, d, *J* 5.2 Hz, C$_4$*H*), 5.07 (1H, t, *J* 2.4 Hz, *H*COCHC=O), 5.21 (2H, dd, *J* 8.2, 5.2 Hz, C$_3$*H* and *H*COCH$_2$COOMe), 7.03–7.43 (10H, m, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 20.9, 61.8, 70.6, 73.7, 77.2, 78.3, 78.8, 81.0, 83.1, 86.2, 117.5, 124.5, 128.1, 128.6, 129.1, 133.4, 137.1, 163.3, 170.0; MS: *m*/*z* 410 (M^+).

4.1.19. (3*S*,3a*R*,6*R*,6a*R*)-6-((3*R*,4*S*)-1-(4-Chlorophenyl)-2-oxo-4-phenylazetidin-3-yloxy)hexahydrofuro[3,2-*b*]-furan-3-yl acetate (16b). A single diastereomer was obtained by flash column chromatography; yield 68%; thick oil [Found: C, 62.16; H, 4.87; N, 3.08; Cl, 7.91. $C_{23}H_{22}NO_6Cl$ requires C, 62.24; H, 4.99; N, 3.15; Cl, 7.99%]; R_f (30% ethyl acetate/petroleum ether) 0.44; $[\alpha]_D^{26}$ +73 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 1747, 1737, 1494, 1244 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.15 (3H, s, COOC*H*$_3$), 3.74–4.15 (4H, m, OCHC*H*$_2$ and OC*H*$_2$CH), 4.55–4.66 (2H, m, OC*H*CH and OC*H*CHAc), 4.68 (1H, d, *J* 4.8 Hz, C$_4$*H*), 4.90 (1H, t, *J* 3.8 Hz, *H*COCHC=O), 5.18–5.26 (2H, m, C$_3$*H* and *H*COCH$_2$COOMe), 7.33–7.48 (9H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 20.9, 64.0, 70.2, 73.9, 77.2, 78.0, 78.3, 85.9, 86.0, 90.2, 118.8, 126.1, 129.1, 129.4, 129.6, 135.4, 135.6, 163.7, 170.0; MS: *m*/*z* 444 (M^+).

4.1.20. (3*S*,3a*R*,6*R*,6a*R*)-3-(Allyloxy)-6-methoxy-hexahydrofuro[3,2-*b*]furan (20). To a solution of 2-*O*-methyl-5-*O*-hydroxy-1,4:3,6-dianhydro-D-glucitol **19** (3.7 g, 23.12 mmol) in freshly distilled allyl bromide (40 mL) were added Ag_2O (7.07 g, 30.52 mmol) and $CaSO_4$ (15 g). The resulting suspension was stirred for 2 days in the dark at room temperature, then diluted with ether (100 mL), filtered through Celite and concentrated under reduced pressure to give the crude product as a brown oil. It was purified by column chromatography (20% ethyl acetate/petroleum ether) to get 2-*O*-methyl-5-*O*-allyl-1,4:3,6-dianhydro-D-glucitol **20** (4.54 g, 98%) as a pale yellow oil [Found: C, 59.87; H, 7.95. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%]; R_f (40% ethyl acetate/petroleum ether) 0.64; $[\alpha]_D^{26}$ +91 (*c* 0.37, $CHCl_3$); ν_{max} (neat) 1735, 1647, 1463, 1220 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.46 (3H, s, OC*H*$_3$), 3.52–3.63 (1H, m, OC*H*CH), 3.87–4.05 (7H, m, OCHC*H*$_2$, OC*H*$_2$CH, OC*H*CHO-olefin and OC*H*$_2$CH=C), 4.52 (1H, dd, *J* 4.2, 1.0 Hz, *H*COMe), 4.67 (1H, t, *J* 4.2 Hz, *H*CO-olefin), 5.15–5.33 (2H, m, HC=C*H*$_2$), 5.79–5.98 (1H, m, *H*C=CH$_2$); δ_C (50 MHz, $CDCl_3$) 57.9, 69.4, 70.2, 73.4, 79.6, 81.5, 83.4, 86.0, 117.1, 133.9; MS: *m*/*z* 201 (M^+).

4.1.21. ((3*S*,3a*R*,6*R*,6a*R*)-6-Methoxy-hexahydrofuro[3,2-*b*]furan-3-yloxy)acetic acid (21). 2-*O*-Methyl-5-*O*-allyl-1,4:3,6-dianhydro-D-glucitol **20** (0.5 g, 2.50 mmol) was dissolved in anhydrous acetone (10 mL) and potassium carbonate (0.025 g) was added. This mixture was cooled to

0 °C and then powdered potassium permanganate (1.0 g, 6.32 mmol) was added portionwise with stirring for about 1–2 h at 0–5 °C. The reaction mixture was stirred at room temperature for 3 h and filtered through Buchner funnel. The manganese dioxide residue was washed with acetone and then extracted with hot water (3×10 mL). The aqueous alkaline extract was cooled and acidified with 10% concd HCl, saturated with NaCl and extracted with dichloromethane (3×20 mL). The dichloromethane extract was washed with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get pure *exo*-bicyclic acid **21** (0.280 g, 51%) as colourless oil [Found: C, 49.48; H, 6.40. $C_9H_{14}O_6$ requires C, 49.54; H, 6.46%]; $[\alpha]_D^{26}$ +35.9 (*c* 0.27, $CHCl_3$); ν_{max} (neat) 3469, 1741, 1647, 1463, 1217 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.45 (3H, s, OC*H*$_3$), 3.52–3.63 (1H, m, OC*H*CH), 3.89–4.17 (7H, m, OCHC*H*$_2$, OC*H*$_2$CH, OC*H*CHOCH$_2$COOH and OC*H*$_2$COOH), 4.58 (1H, d, *J* 4.3 Hz, *H*COMe), 4.71 (1H, t, *J* 4.3 Hz, *H*CCH$_2$COOH), 6.62 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 58.2, 69.8, 73.1, 75.7, 79.9, 81.6, 84.9, 85.8, 177.2; MS: *m*/*z* 219 (M^+).

4.1.22. Diastereomeric mixture of β-lactams 22 and 23. To a stirred solution of the *exo*-bicyclic acid **21** (0.145 g, 0.66 mmol), imine **15a** (0.120 g, 0.66 mmol) and dry triethylamine (0.201 g, 1.99 mmol) in anhydrous dichloromethane (10 mL), a solution of triphosgene (0.098 g, 0.33 mmol) in dichloromethane was added dropswise at 0 °C. The reaction mixture was allowed to come to room temperature and stirred at this temperature for 15 h. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (3×10 mL), saturated bicarbonate solution (3×10 mL) and brine (15 mL), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to get the crude product as a yellow solid. It was purified by flash column chromatography (30% ethyl acetate/petroleum ether) to get diastereomeric mixture of β-lactams **22** and **23** (0.180 g, 71%). After recrystallization through methanol, it was obtained as a white solid, which was an inseparable diastereomeric mixture of β-lactams (50:50); R_f (30% ethyl acetate/petroleum ether) 0.60; mp 175–176 °C; ν_{max} ($CHCl_3$) 1757, 1500, 1338 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.27 (1H, dd, *J* 10.3, 2.0 Hz, OC*H*$_a$CH), 3.37 (3H, s, OC*H*$_3$), 3.41 (3H, s, OC*H*$_3$), 3.42–3.54 (3H, m, OCHC*H*$_2$, OCH$_a$*H*$_b$CH), 3.68–3.72 (1H, m, OC*H*$_a$H$_b$CH), 3.77–4.02 (9H, m, OCHC*H*$_2$, OC*H*$_2$CH, OC*H*$_b$CH, OCHC*H*$_a$, OCHC*H*$_b$, *H*$_a$COCHC=O and C$_4$*H*$_a$), 4.52 (1H, t, *J* 4.2 Hz, *H*$_b$COCHC=O), 4.59 (1H, d, *J* 4.2 Hz, C$_4$*H*$_b$), 5.05 (2H, dd, *J* 13.3, 4.7 Hz, C$_3$*H*$_a$ and *H*$_a$COMe), 5.25 (2H, dd, *J* 7.5, 4.7 Hz, C$_3$*H*$_b$ and *H*$_b$COMe), 7.24–7.42 (20H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 58.0, 58.1, 62.0, 62.4, 69.6, 69.7, 73.0, 73.4, 77.2, 79.5, 79.9, 81.6, 81.7, 82.7, 83.3, 84.6, 85.6, 85.9, 86.0, 117.6, 124.6, 128.0, 128.3, 128.6, 128.8, 128.9, 129.1, 133.1, 133.5, 136.9, 163.6, 163.8.

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19. This molecular structure is drawn by using software programme Chem 3D Pro.
20. The purity of all new β-lactams was determined by HPLC: HP-1050 Ti series pump; detector: JASCO 970 (at 254 nm) connected to integrator: HP-3396 series-II; column: Chromsphere Chromsep 5 C-18, 250×4.6 mm (5 μm); solvent system (v/v): MeCN/H_2O (60:40), flow rate 1.5 mL/min.
21. X-ray diffraction data for compound **9a**: Single crystals of the compound **9a** were grown by slow evaporation of ethyl acetate and petroleum ether (8:2) solution. Colourless cubes of approximate size 0.45×0.40×0.40 mm were used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo Kα radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance was 6.05 cm, 512×512 pixels/frame, hemisphere data acquisition. Total scans=3, total frames=1271, oscillation/frame −0.3°, exposure/frame=5.0 s/frame, maximum detector swing angle=−30.0°, beam centre=(260.2, 252.5), in plane spot width=1.24, SAINT integration, θ range=2.23–25.00°, completeness to θ of 25.00° is 99.9%. $C_{18}H_{23}NO_6$, M=349.37. Crystals belong to orthorhombic, space group $P2_12_12_1$, a=12.4688(7), b=10.7999(6), c=13.3993(8) Å, V=1804.4(2) Å^3, Z=4, D_c=1.286 Mg/m^3, μ(Mo Kα)=0.097 mm^{-1}, T=293(2) K, out of 9153 collected, 3170 are unique reflections [$I>2\sigma(I)$]. All the data were corrected for Lorentzian, polarization and absorption effects. The structure was solved by direct methods using SHELXTL. SHELX-97 (ShelxTL)[22] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Least squares refinement of scale, positional and anisotropic thermal parameters for non-hydrogen atom converged to R=0.0406, $wR2$=0.0985 for 3170 unique observed reflections. X-ray analysis revealed the stereochemistry of the compound to be 3*S*, 4*R* at C3 and C4, respectively. The crystal structure for **9a** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 606925.
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27. X-ray diffraction data for compound **16a**: X-ray structure determination of $C_{23}H_{23}NO_6$: colourless needles 0.33×0.02×0.02 mm grown from methanol. M=409.42, orthorhombic, $P2_12_12_1$, a=6.623(2) Å, b=9.627(3) Å, c=32.182(10) Å, V=2052.0(12) Å^3, Z=4, D=1.325 Mg/m^3, μ=0.096 mm^{-1}, F(000)=864, T=293 K. Data were collected on SMART APEX CCD single crystal X-ray diffractometer using Mo Kα radiation (λ=0.7107 Å) to a maximum θ range of 23.49°. The structure was solved by direct methods using SHELXTL.[22] Least squares refinement of scale, positional and anisotropic thermal parameters for non-hydrogen atom converged to R=0.0898, Rw=0.1746 for 3039 unique observed reflections. Hydrogen atoms were geometrically fixed. The refinements were carried out using SHELXL-97. X-ray analysis revealed the stereochemistry of the compound to be 3*R*, 4*S* at C3 and C4, respectively. The crystal structure for **16a** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 620045.