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Stereoselective synthesis of spiro-β-lactams using D-(+)-glucose derived chiral pool: remarkable influence of the torquoelectronic effect

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Abstract—Diastereoselective synthesis of spiro-β-lactams via [2+2] cycloaddition reaction of imines and chiral ketenes is described. The chiral ketene was prepared from commercially available, inexpensive D-glucose. Although, theoretically four diastereomers are possible, the reaction yielded only two diastereomers stereoselectively in good to moderate yields. The stereochemical outcome of the reaction was in accordance with the torquoelectronic model.

1. Introduction

β-Lactams, being a structural motif in most widely used antibiotics,[1] have occupied a pivotal position in medicinal chemistry for almost a century now. With the microorganisms retaliating the traditional antibiotics via β-lactamase enzymes, the need for novel antibiotics prevails making synthesis of newer β-lactams ever more important. Besides their use as antibiotics, β-lactams are increasingly being used as synthons for biologically important molecules.[2] Apart from this, the recent literature has seen a spurt in the number of other diverse applications of the β-lactams. They have been shown to increase the expression of glutamate transporters through gene activation.[3] β-Lactams have also been found to act as cholesterol acyl transferase inhibitors,[4] thrombin inhibitors,[5] human cytomegalovirus protease inhibitors,[6] matrix metalloprotease inhibitors,[7] human leucocyte elastase,[8] cysteine protease,[9] and apoptosis inductors[10]. Thus, owing to their ever growing applications, synthesis of β-lactams remains a field of incessant activity. In particular, spirocyclic β-lactams have attracted attention as they have been shown to be β-turn mimetics[11] and precursors for α,α-disubstituted β-amino acids.[12] The spiro-β-lactam moiety forms a part of the chartelline, a family of marine natural products.[13] Spiro-β-lactams have also been found to act as poliovirus and human rhinovirus 3C-proteinases inhibitors.[14] They have also found application as cholesterol absorption inhibitors.[15]

Several syntheses of spiro-β-lactams are available in the literature.[16] Many of them have employed the [2+2] cyclocondensation of ketenes and imines,[17] better known as the Staudinger reaction. The reason for the widespread use of the Staudinger reaction is that it scores over other methods in operational simplicity and the actual stereochemical outcomes are often in good concordance with the predicted ones. A large body of literature is available reporting the use of carbohydrates as chiral starting materials for the synthesis of β-lactams.[18] Our group has also been engaged in the stereoselective synthesis of β-lactams using carbohydrates as a source of chirality.[19] Herein, we wish to disclose our work on synthesis of spirocyclic β-lactams using a D-(+)-glucose derived chiral acid and the stereochemical implications of the same. Spirocyclic β-lactams derived from carbohydrates can also be perceived to undergo other transformations as the β-lactams are prone to amide bond cleavage.

2. Results and discussion

The commercially available D-(+)-glucose was used to prepare aldehyde **4** in good yield by following a reported procedure[20] (Scheme 1). This aldehyde was subjected to oxidation[21] using freshly prepared silver oxide to get the desired chiral acid **5**. It was converted to the corresponding

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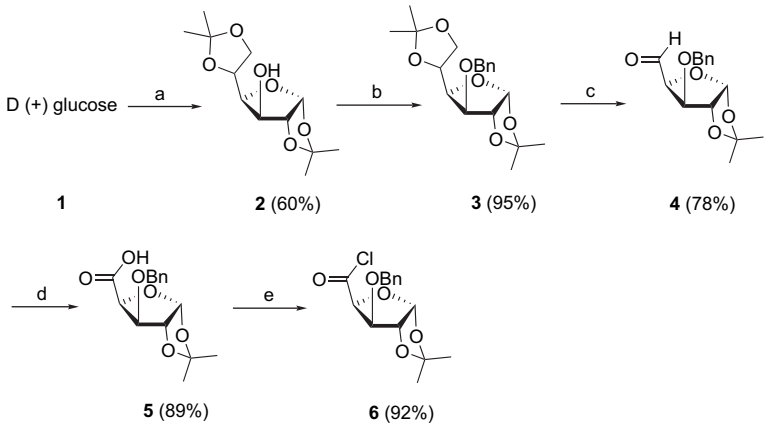
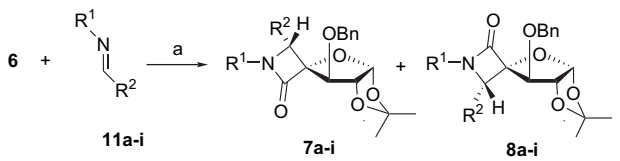


Scheme 1. Reagents and conditions: (a) dry acetone, anhyd $CuSO_4$, concd H_2SO_4, rt, 48 h; (b) NaH, BnBr, dry DMF, 0 °C to rt, 3 h; (c) (i) 75% CH_3COOH, 70 °C, 3 h; (ii) silica gel, 0.65 M, aq $NaIO_4$, DCM, rt, 2 h; (d) $AgNO_3$, aq KOH, HCl, rt, 1 h; (e) $(COCl)_2$, dry DCM, reflux, 4 h.

acid chloride **6** by refluxing with oxalyl chloride in dichloromethane. This acid chloride **6** was then used as a ketene precursor in the Staudinger cycloaddition reaction (Scheme 2) with imines. The reaction proceeded cleanly to afford a diastereomeric mixture of spirocyclic β-lactams **7a–i** and **8a–i** in good yields (Table 1). The ^{1}H NMR spectrum of the crude reaction product revealed a 70:30 mixture of two diastereomers (**7a** and **8a**). Although, theoretically four diastereomers are possible, the formation of only two diastereomers clearly indicates a high level of stereoselectivity in the cycloaddition reaction. Both the diastereomers were separated by careful flash column chromatography. They exhibited a band at around 1755 cm^{-1} in the IR spectrum, typical of a β-lactam carbonyl. In the ^{1}H NMR spectrum of major isomer **7a**, the C-3 proton of the β-lactam ring resonated at δ 5.40, two singlets at δ 1.35 and δ 1.73 showed the presence of acetonide group and the anomeric proton appeared as a doublet at δ 5.50 indicating the presence of carbohydrate moiety in the molecule. Similarly, the minor isomer **8a** showed the β-lactam C-3 proton at δ 4.82 along with other signals for the carbohydrate moiety. The stereochemistry of both the diastereomers **7a** and **8a** was elucidated with the help of NOE experiments. In the major diastereomer **7a**, the only proton on the β-lactam ring (C_3H) showed NOE interactions with C_8H and the ortho protons of the aromatic ring (C_3-PMP) on the same carbon (Figs. 1 and 3). In the minor diastereomer **8a**, C_3H proton, apart from a strong interaction (Figs. 1 and 3) with C_8H and with the aromatic protons similar to the major isomer **7a**, also showed interaction (Figs. 2 and 3) with one of the methyl protons from the 6,7-*O*-isopropylidene group, which was absent in the major isomer **7a**. This is indicative of the fact that the β-lactam C-3 of **8a** is on the same side of the acetonide group. Hence, based on the NOE results, structures **7**(3*R*,4*R*) and **8**(3*S*,4*S*) (Fig. 3) were assigned to the major and minor diastereomers, respectively. Furthermore, we carried out C_8-O-debenzylation on some of the spiro-β-lactams. Gratifyingly, we could get good crystals after C_8-O-debenzylation of one of the major isomers **7c**. A single crystal X-ray diffraction analysis[22] of debenzylated product **12c** (Fig. 4) confirmed the stereochemistry inferred by NOE experiments.



Scheme 2. Reagents and conditions: (a) Et_3N, dry DCM, −40 °C to rt, 15 h.

Having elucidated the stereochemistry of the newly formed stereocenters in both the diastereomers, we set out to account for the observed stereochemical results. The mechanism of the Staudinger reaction has been a subject of extensive investigation.[23] It is believed that the imine attacks the ketene from the less hindered side. Study of the literature brought forth some reports providing a mechanistic rationale for the stereochemistry of spiro-β-lactams obtained by the Staudinger reaction.[17d,24] In a report on proline derived spiro-β-lactams,[24] the observed stereochemistry of the β-lactams is ascribed to the attack of imine taking place from the less hindered side of ketene. In that case, the steric bulk on the nitrogen diverts the attack of the imine toward the less hindered side of the ketene. During the study of the Staudinger reaction of ketenes derived from 2- and 3-tetrahydrofuroyl chloride,[17d] the torquoelectronic effect has been invoked to explain the differences in stereochemical outcome. The oxygen atom of the 2-tetrahydrofuroyl chloride derived ketene prefers an outward position in the ring closure step, thereby repelling the attack of imine toward the opposite side of the ketene. Although this ketene exhibits torquoelectronic effects, the two sides of the ketene (–O–, –CH_2–) are not much differentiated sterically.

Table 1. Synthesis of spiro-β-lactams **7a–i** and **8a–i**

7 and **8**	R^1	R^2	Yield[a] (%)	Isomers[b] (**7**:**8**)
A	PMP	PMP[c]	65	70:30
B	Ph	PMP	71	72:28
C	Ph	Ph	62	70:30
D	PMP	Ph	62	68:32
E	4-Cl-Ph	Ph	59	65:35
F	Ph	Styryl	69	71:39
G	PMP	Styryl	67	68:32
H	4-Me-Ph	Ph	72	64:36
I	Ph	*p*-Tolyl	70	64:36

[a] Isolated yields of diastereomeric mixture.
[b] Ratio of diastereomers was determined by ^{1}H NMR.
[c] PMP=*p*-Methoxyphenyl.

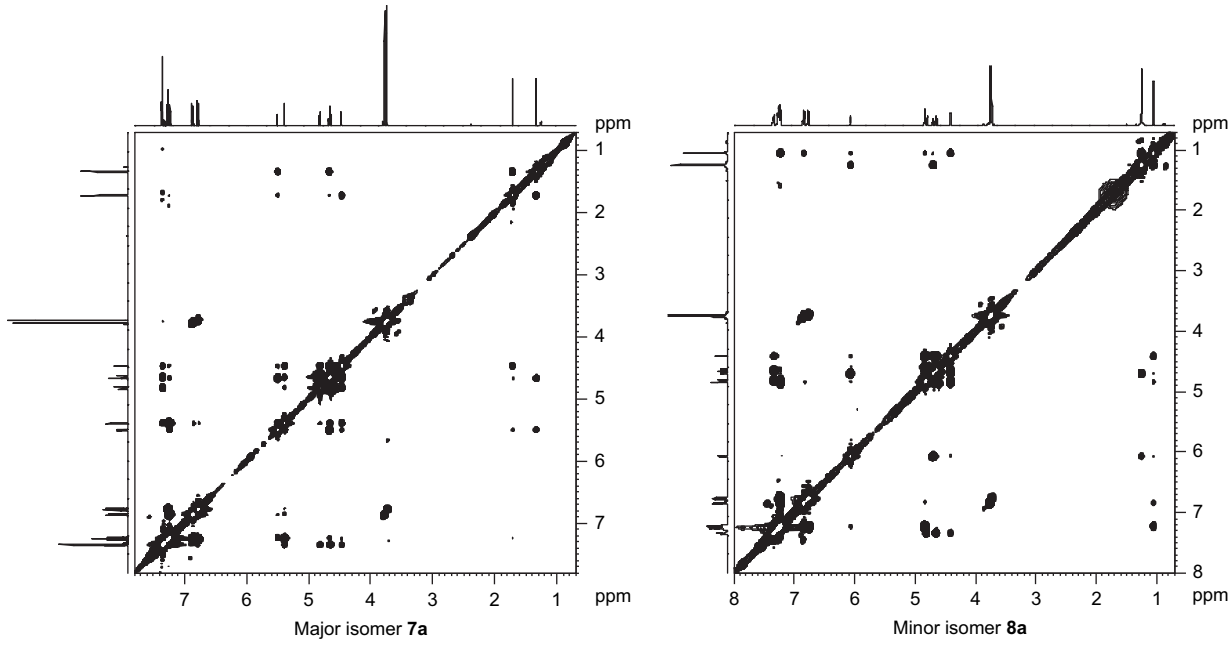


Figure 1. NOESY spectra for **7a** (major) and **8a** (minor) isomers.

In this context, it would be interesting to imagine a case wherein the steric and torquoelectronic factors counter each other. Our present study makes a case in point. Considering the starting imine to be having *E* configuration and the approach toward the ketene to be from two different sides, four products are possible. Figure 5 shows the approach of the imine from all possible directions. In the case of pathways 1 and 2, the imine attacks from the opposite side of the furanose oxygen delivering two products **7**(3*R*,4*R*), **8**(3*S*,4*S*) via a conrotatory ring closure (Fig. 5). Pathways 3 and 4 represent an attack of the imine from the side of the furanose oxygen giving rise to compounds **9**(3*S*,4*R*) and **10**(3*R*,4*S*). With the C_8 bearing a benzyloxy group, steric factors state that attack of the imine should take place from the opposite side (Fig. 5) resulting in formation of compounds **9**(3*S*,4*R*) and **10**(3*R*,4*S*). Whereas, with the torquoelectronic factors governing the course of reaction, attack should happen from opposite side of the furanose oxygen (pathways 1 and 2), delivering compounds **7**(3*R*,4*R*) and **8**(3*S*,4*S*). In pathway 1, after the initial attack of the imine

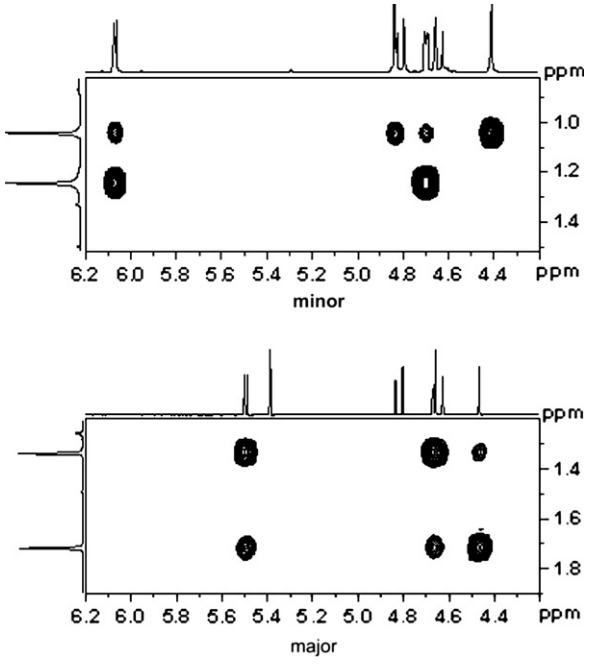


Figure 2. 2D NOESY spectra showing interaction of C_3H with acetonide group in minor isomer **8a** (above) and absence of this interaction in major isomer **7a** (below).

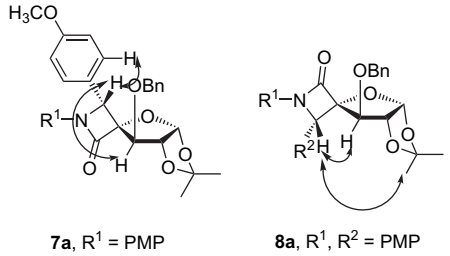


Figure 3. NOE interactions in major isomer **7a** and minor isomer **8a**.

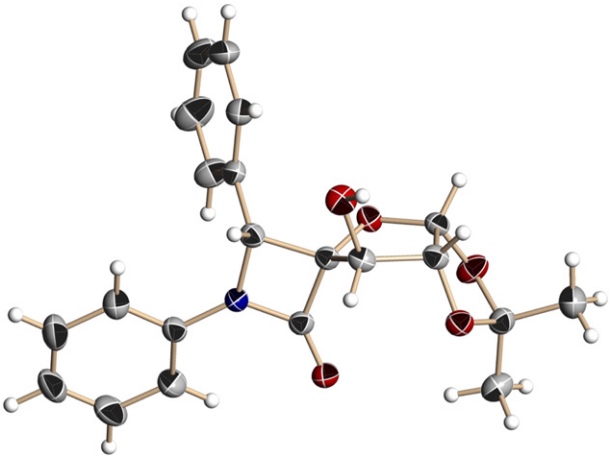


Figure 4. ORTEP diagram of compound **12c**.

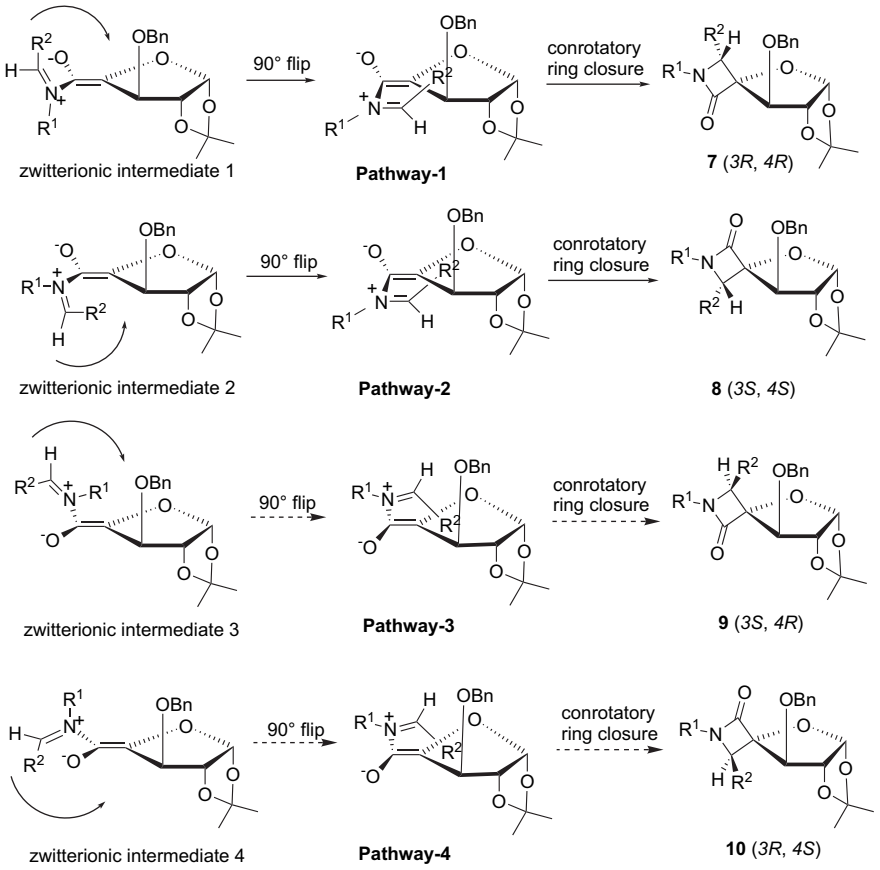


Figure 5. Plausible mechanism for explaining the observed stereochemical outcomes.

resulting in formation of a zwitterionic intermediate 1, the next step (90° flip) in which the imine part attains coplanarity with the ketene should proceed with some resistance from the benzyloxy substituent on the α-carbon (C-8) of the ketene. This should divert the attack of the imine to the other side (pathways 3 and 4) of the ketene; at least in part, if not exclusively. But defying the steric constraints, reaction showed strong inclination toward delivering products governed by the torquoelectronic effect. With the structures of the actual products found to be **7** and **8**, it is pretty clear that the torquoelectronic factor exerts a stronger effect in the reaction. Each side of the ketene is additionally differentiated into two faces: top face (pathways 1 and 3) and bottom face (pathways 2 and 4). Among the two diastereomers, **7** (pathway 1) was found to be major and **8** was the minor (pathway 2), although the diastereoselectivity was only moderate (Table 1). This can be rationalized by proposing that the bulky 6,7-*O*-isopropylidene moiety, to some extent, prevents the attack of the imine from bottom face, so that the zwitterionic intermediate 2 (pathway 2) is formed to a lesser extent than the zwitterionic intermediate 1 (pathway 1) resulting in the observed proportion of diastereomers.

3. Conclusion

A stereoselective synthesis of spirocyclic β-lactams from a D-(+)-glucose derived chiral acid has been achieved. The reaction showed strong propensity toward following a course governed by the torquoelectronic effect. Although four diastereomers are possible, only two diastereomers were obtained with the imine attacking from the hindered side illustrating the strong influence of the torquoelectronic effect. The facial selectivity was moderate. Work to exploit the densely functionalized nature of the product and cleavability of the lactam to transform it into other heterocycles is underway.

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 a Perkin–Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Buchi melting point apparatus and are 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*, fragentor 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.

4.2. (−)-(2*S*,3*R*,4*R*,5*R*)-3-Benzyloxy-4,5-*O*-isopropylidene-tetrahydro-furan-2-carboxylic acid (5)

To the aldehyde **4** (0.566 g, 2.02 mmol) was added an aqueous solution of $AgNO_3$ (0.588 M, 8.91 mL). To the resulting

emulsion was added aqueous KOH solution (0.91 M, 11.4 mL). A dark black precipitate was formed, which was stirred for further an hour. It was then filtered through a Buchner funnel. The filtrate was cooled to 0 °C and acidified with approximately 6 M aqueous HCl to *p*H=2. The acidified solution was then extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and concentrated under reduced pressure to give acid **5** (0.490 g, 82%) as a white solid. Mp 140–141 °C; [Found: C, 61.38; H, 6.05. $C_{15}H_{18}O_6$ requires: C, 61.21; H, 6.16%.] $[\alpha]_D^{26}$ −54.5 (*c* 1.76, $CHCl_3$); ν_{max} ($CHCl_3$): 3300–2800, 1733 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.26 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 4.25–4.81 (5H, m, C_2–*H*, C_3–*H*, C_4–*H*, O–C*H*$_2$–Ph), 6.02 (1H, d, *J* 3.6 Hz, C_5–*H*), 7.16–7.29 (5H, m, Ar–*H*), 10.2 (1H, br s, –COO*H*); δ_C (50 MHz, $CDCl_3$): 26.2, 26.9, 72.5, 79.5, 81.8, 82.2, 105.7, 112.7, 127.7, 128.0, 128.4, 136.5, 171.8. MS: *m*/*z* 295 (M+1).

4.3. (−)-(2*S*,3*R*,4*R*,5*R*)-3-Benzyloxy-4,5-*O*-isopropylidene-tetrahydro-furan-2-carboxylic acid chloride (6)

Acid **5** (0.500 g, 1.70 mmol) was dissolved in 10 mL anhydrous dichloromethane and cooled to 0 °C. To the cooled solution was added oxalyl chloride (0.215 g, 1.70 mmol) dropwise. The resultant solution was refluxed for 5 h. After 5 h, the solution was cooled to room temperature and used directly for preparation of spiro-β-lactams.

4.4. General procedure for the synthesis of spiro-β-lactams

A solution of acid chloride **6** (0.259 g, 0.826 mmol) in anhydrous dichloromethane (10 mL) was added to a precooled solution of imine **11a** (0.116 g, 0.550 mmol) and anhydrous triethylamine (0.344 mL, 2.47 mmol) in anhydrous dichloromethane (15 mL) at −40 °C over a period of 15–20 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. After completion of reaction (TLC), the reaction mixture was diluted with dichloromethane and washed successively with water (3×10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude product as a dark brown viscous liquid (0.304 g, 71%). The crude reaction mixture was purified using flash column chromatography (20% ethyl acetate–petroleum ether) to get two diastereomers **7a** and **8a**.

4.4.1. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-bis(4-methoxyphenyl)-5-oxa-2-aza-spiro-[3.4]octan-1-one (7a). Yield 52%; thick oil; [Found: C, 69.80; H, 6.09; N, 2.60. $C_{30}H_{31}NO_7$ requires: C, 69.62; H, 6.03; N, 2.71%.] R_f (20% ethyl acetate/petroleum ether): 0.35; $[\alpha]_D^{26}$ −54.5 (*c* 1.1, $CHCl_3$); ν_{max} (neat): 1759 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.35 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 3.75 (3H, s, Ar–OC*H*$_3$), 3.80 (3H, s, Ar–OC*H*$_3$), 4.47 (1H, d, *J* 1.2 Hz, C_8–*H*), 4.62–4.68 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.83 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 5.40 (1H, s, C_3–*H*), 5.50 (1H, d, *J* 4.1 Hz, C_6–*H*), 6.79 (2H, d, *J* 9.1 Hz, Ar–*H*), 6.87 (2H, d, *J* 8.7 Hz, Ar–*H*), 7.23–7.36 (9H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.9, 27.0, 55.2, 55.4, 61.9, 72.7, 83.2, 83.9, 95.3, 105.3, 113.9, 114.2, 114.3, 118.8, 125.3, 127.6, 128.1, 128.5, 129.0, 130.6, 136.9, 156.2, 159.6, 163.6; MS: *m*/*z* 518 (M+1).

4.4.2. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-bis(4-methoxyphenyl)-5-oxa-2-aza-spiro-[3.4]octan-1-one (8a). Yield 19%; white solid; mp 147–148 °C; [Found: C, 69.52; H, 5.87; N, 2.58. $C_{30}H_{31}NO_7$ requires: C, 69.62; H, 6.03; N, 2.71%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −30.9 (*c* 1.1, $CHCl_3$); ν_{max} (neat): 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.03 (3H, s, C*H*$_3$), 1.23 (3H, s, C*H*$_3$), 3.72 (3H, s, Ar–OC*H*$_3$), 3.75 (3H, s, Ar–OC*H*$_3$), 4.40 (1H, d, *J* 1.2 Hz, C_8–*H*), 4.60–4.70 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.81 (1H, d, *J* 12.4 Hz, 1°C*H*′$_2$–Ph), 4.82 (1H, s, C_3–*H*), 6.06 (1H, d, *J* 4.0 Hz, C_6–*H*), 6.76 (2H, d, *J* 9.1 Hz, Ar–*H*), 6.83 (2H, d, *J* 8.7 Hz, Ar–*H*), 7.19–7.36 (9H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.3, 26.7, 55.0, 55.3, 66.5, 72.4, 83.9, 85.4, 94.7, 106.2, 113.7, 113.8, 114.0, 114.3, 118.9, 125.2, 127.8, 128.4, 129.8, 130.3, 137.0, 156.2, 159.9, 163.3; MS: *m*/*z* 518 (M+1).

4.4.3. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-(4-methoxyphenyl)-2-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (7b). Yield 45%; thick oil; [Found: C, 71.38; H, 5.84; N, 2.98. $C_{29}H_{29}NO_6$ requires: C, 71.44; H, 5.99; N, 2.87%.] R_f (20% ethyl acetate/petroleum ether): 0.30; $[\alpha]_D^{26}$ −50 (*c* 1, $CHCl_3$); ν_{max} (neat): 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.27 (3H, s, C*H*$_3$), 1.65 (3H, s, C*H*$_3$), 3.71(3H, s, Ar–OC*H*$_3$), 4.40 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.54–4.61 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.75 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 5.35 (1H, s, C_3–*H*), 5.44 (1H, d, *J* 4.0 Hz, C_6–*H*), 6.77–7.03 (3H, m, Ar–*H*), 7.14–7.29 (11H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 25.8, 26.3, 55.4, 65.9, 72.0, 84.2, 85.1, 94.3, 105.4, 114.2, 117.3, 124.8, 125.4, 126.7, 127.8, 128.2, 128.7, 129.2, 129.8, 137.0, 137.1, 159.6, 163.9; MS: *m*/*z* 488 (M+1).

4.4.4. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-(4-methoxyphenyl)-2-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (8b). Yield 20%; thick oil; [Found: C, 71.58; H, 5.79; N, 2.80. $C_{29}H_{29}NO_6$ requires: C, 71.44; H, 5.99; N, 2.87%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −35.8 (*c* 0.78, $CHCl_3$); ν_{max} (neat): 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.99 (3H, s, C*H*$_3$), 1.18 (3H, s, C*H*$_3$), 3.69 (3H, s, Ar–OC*H*$_3$), 4.35 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.52–4.64 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.73 (1H, d, *J* 12.4 Hz, OC*H*′$_2$–Ph), 4.80 (1H, s, C_3–*H*), 6.01 (1H, d, *J* 3.9 Hz, C_6–*H*), 6.76–7.01 (3H, m, Ar–*H*), 7.12–7.30 (11H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.4, 26.8, 55.1, 66.4, 72.6, 84.0, 85.5, 94.7, 106.3, 113.9, 117.7, 124.2, 125.1, 126.8, 127.9, 128.0, 128.5, 129.0, 129.8, 136.9, 137.0, 160.0, 164.1; MS: *m*/*z* 488 (M+1).

4.4.5. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-diphenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (7c). Yield 43%; thick oil; [Found: C, 73.31; H, 6.10; N, 3.20. $C_{28}H_{27}NO_5$ requires: C, 73.50; H, 5.94; N, 3.06%.] R_f (20% ethyl acetate/petroleum ether): 0.30 $[\alpha]_D^{26}$ −75 (*c* 1.44, $CHCl_3$); ν_{max} (neat): 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.29 (3H, s, C*H*$_3$), 1.67 (3H, s, C*H*$_3$), 4.43 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.58–4.64 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.79 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 5.43 (1H, s, C_3–*H*), 5.46 (1H, d, *J* 4.1 Hz, C_6–*H*), 6.98–7.33 (15H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.8, 26.9, 62.2, 72.7, 83.1, 83.7, 95.5, 105.5,

114.2, 117.4, 124.2, 127.5, 127.6, 128.1, 128.3, 128.4, 128.5, 128.9, 133.4, 136.7, 137.0, 164.2; MS: *m/z* 458 (M+1).

4.4.6. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2,3-diphenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (8c). Yield 19%; thick oil; [Found: C, 73.59; H, 6.09; N, 3.14. $C_{28}H_{27}NO_5$ requires: C, 73.50; H, 5.94; N, 3.06%.] R_f (20% ethyl acetate/petroleum ether): 0.20 $[\alpha]_D^{26}$ −42.1 (*c* 1.3, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.35 (3H, s, CH_3), 1.52 (3H, s, CH_3), 4.42 (1H, d, *J* 1.2 Hz, C_8–*H*), 4.61–4.67 (2H, m, OCH_2–Ph, C_7–*H*), 4.80 (1H, d, *J* 12.4 Hz, 1CH'_2–Ph), 4.81 (1H, s, C_3–*H*), 6.02 (1H, d, *J* 4.0 Hz, C_6–*H*), 7.01–7.33 (15H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.4, 26.9, 62.0, 72.9, 83.4, 84.0, 94.8, 104.4, 115.1, 117.7, 123.8, 127.5, 127.6, 128.5, 128.7, 128.8, 129.2, 129.4, 132.9, 136.7, 137.2, 165.5; MS: *m/z* 458 (M+1).

4.4.7. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (7d). Yield 42%; thick oil; [Found: C, 71.61; H, 5.81; N, 2.77. $C_{29}H_{29}NO_6$ requires: C, 71.44; H, 5.99; N, 2.87%.] R_f (20% ethyl acetate/petroleum ether): 0.30; $[\alpha]_D^{26}$ −80.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.26 (3H, s, CH_3), 1.63 (3H, s, CH_3), 3.66 (3H, s, Ar–OCH_3), 4.41 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.55–4.60 (2H, m, OCH_2–Ph, C_7–*H*), 4.76 (1H, d, *J* 11.6 Hz, OCH'_2–Ph), 5.36 (1H, s, C_3–*H*), 5.41 (1H, d, *J* 4.0 Hz, C_6–*H*), 6.67–6.74 (2H, m, Ar–*H*), 7.14–7.30 (12H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.9, 27.0, 55.4, 62.3, 72.8, 83.2, 83.9, 95.5, 105.4, 114.3, 118.8, 126.4, 127.6, 127.7, 128.2, 128.3, 128.5, 128.6, 130.6, 133.6, 136.9, 156.3, 163.6; MS: *m/z* 488 (M+1).

4.4.8. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (8d). Yield 20%; thick oil; [Found: C, 71.48; H, 6.10; N, 2.93. $C_{29}H_{29}NO_6$ requires: C, 71.44; H, 5.99; N, 2.87%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −71.2 (*c* 1.1, $CHCl_3$); ν_{max} (neat): 1756 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.37 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.83 (3H, s, Ar–OCH_3), 4.37 (1H, d, *J* 1.2 Hz, C_8–*H*), 4.61–4.72 (2H, m, OCH_2–Ph, C_7–*H*), 4.82 (1H, d, *J* 12.4 Hz, OCH'_2–Ph), 4.90 (1H, s, C_3–*H*), 6.01 (1H, d, *J* 4.0 Hz, C_6–*H*), 6.69–6.74 (2H, m, Ar–*H*), 7.17–7.32 (12H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.1, 26.4, 54.9, 62.5, 72.7, 83.2, 83.8, 95.4, 104.9, 114.1, 119.3, 126.8, 127.6, 127.7, 128.1, 128.3, 128.4, 128.7, 130.5, 133.7, 136.7, 156.5, 165.1; MS: *m/z* 488 (M+1).

4.4.9. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-2-(4-chlorophenyl)-6,7-*O*-isopropylidene-3-phenyl-5-oxa-2-aza-spiro-[3.4]octan-1-one (7e). Yield 38%; thick oil; [Found: C, 68.51; H, 5.44; N, 2.68; Cl, 7.35. $C_{28}H_{26}NO_5Cl$ requires: C, 68.35; H, 5.32; N, 2.84; Cl, 7.20%.] R_f (20% ethyl acetate/petroleum ether): 0.40; $[\alpha]_D^{26}$ −63.6 (*c* 1.1, $CHCl_3$); ν_{max} (neat): 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.26 (3H, s, CH_3), 1.63 (3H, s, CH_3), 4.40 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.54–4.60 (2H, m, OCH_2–Ph, C_7–*H*), 4.77 (1H, d, *J* 11.6 Hz, OCH'_2–Ph), 5.35 (1H, s, C_3–*H*), 5.44 (1H, d, *J* 4.0 Hz, C_6–*H*), 7.15–7.28 (14H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.8, 26.9, 62.5, 72.9, 83.2, 83.8, 95.8, 105.6, 114.4, 118.7, 127.6, 128.2, 128.5, 128.6, 128.7, 129.1, 129.4, 133.0, 135.5, 136.7, 164.2; MS: *m/z* 492 (M+1).

4.4.10. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-2-(4-chlorophenyl)-6,7-*O*-isopropylidene-3-phenyl-5-oxa-2-aza-spiro-[3.4]octan-1-one (8e). Yield 21%; thick oil; [Found: C, 68.48; H, 5.43; N, 2.72; Cl, 7.43. $C_{28}H_{26}NO_5Cl$ requires: C, 68.35; H, 5.32; N, 2.84; Cl, 7.20%.] R_f (20% ethyl acetate/petroleum ether): 0.30; $[\alpha]_D^{26}$ −80.0 (*c* 0.9, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.27 (3H, s, CH_3), 1.44 (3H, s, CH_3), 4.35 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.58–4.73 (2H, m, OCH_2–Ph, C_7–*H*), 4.83 (1H, d, *J* 12.3 Hz, OCH'_2–Ph), 4.84 (1H, s, C_3–*H*), 6.0 (1H, d, *J* 4.1 Hz, C_6–*H*), 7.15–7.27 (14H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.3, 26.8, 61.9, 73.1, 83.0, 83.9, 95.4, 105.7, 114.2, 118.7, 127.3, 128.1, 128.5, 128.6, 128.7, 129.0, 129.3, 133.1, 135.4, 136.7, 163.9; MS: *m/z* 492 (M+1).

4.4.11. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-styryl-5-oxa-2-aza-spiro[3.4]octan-1-one (7f). Yield 49%; thick oil; [Found: C, 74.70; H, 6.21; N, 2.77. $C_{30}H_{29}NO_5$ requires: C, 74.51; H, 6.04; N, 2.89%.] R_f (20% ethyl acetate/petroleum ether): 0.35; $[\alpha]_D^{26}$ −16.6 (*c* 1.2, $CHCl_3$); ν_{max} (neat): 1756 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.31 (3H, s, CH_3), 1.69 (3H, s, CH_3), 4.38 (1H, d, *J* 1.2 Hz, C_8–*H*), 4.54 (1H, d, *J* 11.6 Hz, OCH_2–Ph), 4.64 (1H, dd, *J* 3.9, 1.2 Hz, C_7–*H*), 4.74 (1H, d, *J* 11.6 Hz, OCH'_2–Ph), 4.95 (1H, d, *J* 8.8 Hz, C_3–*H*), 5.85 (1H, d, *J* 3.9 Hz, C_6–*H*), 6.28 (1H, dd, *J* 16.1, 8.8 Hz, Ph–CH=C*H*–CH–), 6.71 (1H, d, *J* 16.1 Hz, Ph–C*H*=CH–), 6.98–7.41 (15H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.8, 26.9, 61.5, 72.7, 83.2, 83.7, 95.6, 105.9, 114.4, 117.3, 123.7, 124.3, 126.7, 127.5, 128.1, 128.3, 128.5, 128.6, 129.0, 135.8, 136.3, 136.8, 137.6, 164.0; MS: *m/z* 484 (M+1).

4.4.12. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-styryl-5-oxa-2-aza-spiro[3.4]octan-1-one (8f). Yield 20%; white solid; mp 174–176 °C; [Found: C, 74.63; H, 5.89; N, 3.01. $C_{30}H_{29}NO_5$ requires: C, 74.51; H, 6.04; N, 2.89%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −55.0 (*c* 2, $CHCl_3$); ν_{max} (neat): 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.30 (3H, s, CH_3), 1.37 (3H, s, CH_3), 4.40 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.53 (1H, d, *J* 8.9 Hz, C_3–*H*), 4.55–4.64 (2H, m, OCH_2–Ph, C_7–*H*), 4.69 (1H, d, *J* 12.2 Hz, OCH'_2–Ph), 6.15 (1H, d, *J* 3.7 Hz, C_6–*H*), 6.28 (1H, dd, *J* 15.9, 8.9 Hz, Ph–CH=C*H*–CH–), 6.75 (1H, d, *J* 15.9 Hz, Ph–C*H*=CH–), 7.10–7.50 (15H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.4, 26.7, 62.1, 71.9, 83.5, 83.7, 95.1, 105.3, 113.9, 116.9, 123.5, 124.2, 126.4, 127.4, 128.2, 128.3, 128.5, 128.6, 128.9, 135.5, 136.4, 136.8, 137.7, 166; MS: *m/z* 484 (M+1).

4.4.13. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-styryl-5-oxa-2-aza-spiro-[3.4]octan-1-one (7g). Yield 45%; thick oil; [Found: C, 72.62; H, 6.24; N, 2.55. $C_{31}H_{31}NO_6$ requires: C, 72.49; H, 6.08; N, 2.72%.] R_f (20% ethyl acetate/petroleum ether): 0.30; $[\alpha]_D^{26}$ −26.6 (*c* 0.5, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.38 (3H, s, CH_3), 1.75 (3H, s, CH_3), 3.76 (3H, s, Ar–OCH_3), 4.45 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.58–4.70 (2H, m, OCH_2–Ph, C_7–*H*), 4.80 (1H, d, *J* 11.7 Hz, OCH'_2–Ph), 4.98 (1H, d, *J* 8.8 Hz, C_3–*H*), 5.91 (1H, d, *J* 3.7 Hz, C_6–*H*), 6.35 (1H, dd, *J* 16.0, 8.8 Hz, Ph–CH=C*H*–CH–), 6.83 (1H, d, *J* 16.0 Hz, Ph–C*H*=CH–), 7.20–7.42 (14H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.9, 27.0, 55.4, 61.6, 72.7, 83.2, 83.8, 95.6, 105.8, 114.3, 114.4,

118.7, 123.9, 126.7, 127.5, 128.1, 128.3, 128.6, 131.1, 135.8, 136.3, 136.8, 156.3, 163.3; MS: *m*/*z* 514 (M+1).

4.4.14. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-(4-methoxyphenyl)-3-styryl-5-oxa-2-aza-spiro-[3.4]octan-1-one (8g). Yield 22%; thick oil; [Found: C, 72.55; H, 5.94; N; 2.84. $C_{31}H_{31}NO_6$ requires: C, 72.49; H, 6.08; N, 2.72%.] R_f (20% ethyl acetate/petroleum ether): 0.25; $[\alpha]_D^{26}$ −45.0 (*c* 0.4, $CHCl_3$); ν_{max} (neat): 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.30 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$), 3.77 (3H, s, Ar–OC*H*$_3$), 4.36 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.57 (1H, d, *J* 8.7 Hz, C_3–*H*), 4.64 (1H, d, *J* 12.4 Hz, OC*H*$_2$–Ph), 4.72 (1H, dd, *J* 3.9, 1.0 Hz, C_7–H), 4.77 (1H, d, *J* 12.4 Hz, OC*H*′$_2$–Ph), 6.13 (1H, d, *J* 3.9 Hz, C_6–*H*), 6.26 (1H, dd, *J* 15.9, 8.7 Hz, Ph–CH=C*H*–CH–), 6.71 (1H, d, *J* 15.9 Hz, Ph–C*H*=CH–), 6.84 (2H, d, *J* 9.1 Hz, Ar–*H*), 7.23–7.43 (12H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 26.1, 26.4, 55.4, 65.9, 72.5, 83.7, 85.6, 95.0, 106.6, 113.5, 114.3, 119.0, 123.8, 126.8, 127.9, 128.0, 128.3, 128.5, 128.6, 130.9, 135.8, 137.0, 138.0, 156.4, 162.5; MS: *m*/*z* 514 (M^++1).

4.4.15. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-phenyl-2-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (7h). Yield 46%; thick oil; [Found: C, 74.02; H, 6.02; N, 3.06. $C_{29}H_{29}NO_5$ requires: C, 73.86; H, 6.19; N, 2.97%.] R_f (20% ethyl acetate/petroleum ether): 0.3; $[\alpha]_D^{26}$ −56.6 (*c* 1.2, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.33 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.28 (3H, s, Ar–C*H*$_3$), 4.47 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.65 (1H, d, *J* 11.6 Hz, OC*H*$_2$–Ph), 4.66 (1H, dd, *J* 4.1, 1.1 Hz, C_7–*H*), 4.83 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 5.44 (1H, s, C_3–*H*), 5.48 (1H, d, *J* 4.1 Hz, C_6–*H*), 7.04 (2H, d, *J* 8.4 Hz, Ar–*H*), 7.18–7.35 (12H, m, Ar); δ_C (50 MHz, $CDCl_3$): 20.7, 26.7, 26.8, 62.0, 72.6, 83.0, 83.6, 95.4, 105.4, 114.1, 117.3, 127.5, 127.6, 128.0, 128.1, 128.3, 128.4, 129.4, 133.3, 133.8, 134.5, 136.7, 163.9. MS: *m*/*z* 472 (M+1).

4.4.16. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-3-phenyl-2-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (8h). Yield 26%; thick oil; [Found: C, 73.98; H, 6.33; N, 2.81. $C_{29}H_{29}NO_5$ requires: C, 73.86; H, 6.19; N, 2.97%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −28.8 (*c* 0.9, $CHCl_3$); ν_{max} (neat): 1758 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.34 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 2.33 (3H, s, Ar–C*H*$_3$), 4.42 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.57–4.66 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.79 (1H, d, *J* 12.3 Hz, OC*H*′$_2$–Ph), 4.87 (1H, s, C_3–*H*), 6.06 (1H, d, *J* 3.9 Hz, C_6–*H*), 7.03 (2H, d, *J* 8.1 Hz, Ar–*H*), 7.11–7.47 (12H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 20.8, 26.3, 26.4, 66.6, 72.5, 82.5, 82.6, 94.6, 105.6, 113.9, 117.5, 127.5, 127.6, 127.9, 128.2, 128.3, 128.5, 129.4, 133.5, 133.9, 134.4, 136.7, 163.7. MS: *m*/*z* 472 (M+1).

4.4.17. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (7i). Yield 45%; thick oil; [Found: C, 73.71; H, 6.38; N, 2.92. $C_{29}H_{29}NO_5$ requires: C, 73.86; H, 6.19; N, 2.97%.] R_f (20% ethyl acetate/petroleum ether): 0.35; $[\alpha]_D^{26}$ −40.0 (*c* 0.3, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.33 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.34 (3H, s, Ar–C*H*$_3$), 4.46 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.61–4.71 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.83 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 5.42 (1H, s, C_3–*H*), 5.49 (1H, d, *J* 4.0 Hz, C_6–*H*), 7.01–7.39 (14H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 21.1, 26.8, 26.9, 62.0, 72.7, 83.2, 83.8, 95.3, 105.4, 114.2, 117.5, 124.1, 127.5, 127.6, 128.0, 128.5, 128.9, 129.2, 130.3, 136.8, 137.1, 138.1, 164.3. MS: *m*/*z* 472 (M+1).

4.4.18. (−)-(3*S*,4*S*,6*R*,7*R*,8*R*)-8-Benzyloxy-6,7-*O*-isopropylidene-2-phenyl-3-*p*-tolyl-5-oxa-2-aza-spiro[3.4]octan-1-one (8i). Yield 25%; thick oil; [Found: C, 74.04; H, 6.12; N, 3.12. $C_{29}H_{29}NO_5$ requires: C, 73.86; H, 6.19; N, 2.97%.] R_f (20% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −28.3 (*c* 1.2, $CHCl_3$); ν_{max} (neat): 1755 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.31 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 2.32 (3H, s, Ar–C*H*$_3$), 4.41 (1H, d, *J* 1.0 Hz, C_8–*H*), 4.59–4.67 (2H, m, OC*H*$_2$–Ph, C_7–*H*), 4.78 (1H, d, *J* 11.6 Hz, OC*H*′$_2$–Ph), 4.87 (1H, s, C_3–*H*), 6.06 (1H, d, *J* 4.0 Hz, C_6–*H*), 7.01–7.39 (14H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$): 21.0, 26.3, 26.7, 61.9, 72.1, 83.5, 84.0, 95.5, 104.9, 114.7, 117.3, 124.1, 127.3, 127.6, 128.2, 128.6, 128.9, 129.3, 130.2, 136.7, 137.9, 138.1, 163.8. MS: *m*/*z* 472 (M+1).

4.5. (−)-(3*R*,4*R*,6*R*,7*R*,8*R*)-8-Hydroxy-6,7-*O*-isopropylidene-2,3-diphenyl-5-oxa-2-aza-spiro[3.4]octan-1-one (12c)

O-benzylated spiro-β-lactam **7c** (0.216 g, 0.472 mmol) was dissolved in dry methanol (10 mL). Pd–C (10%, 0.050 g) and ammonium formate (0.90 g, 1.416 mmol) were added to it and the resulting solution was refluxed for 3 h. After completion (TLC), the solution was filtered through a sintered funnel and the residue was washed with methanol. The filtrate was dried over anhydrous $MgSO_4$ and concentrated in vacuo to furnish the crude product. The crude product was recrystallized from ethyl acetate–petroleum ether to obtain pale yellow crystals of debenzylated product **12c** (0.152 g, 88%), which were used for single crystal X-ray analysis; mp 186–188 °C; [Found: C, 68.61; H, 5.89; N, 3.72. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.76; N, 3.81%.] R_f (40% ethyl acetate/petroleum ether): 0.20; $[\alpha]_D^{26}$ −123.52 (*c* 3.4, $CHCl_3$); ν_{max} ($CHCl_3$): 1755, 3352 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.30 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 4.42 (1H, d, *J* 1.1 Hz, C_8–*H*), 4.64 (1H, dd, *J* 4.0, 1.1 Hz, C_7–*H*), 5.53 (1H, s, C_3–*H*), 5.60 (1H, br s, –O*H*), 5.80 (1H, d, *J* 4.0 Hz, C_6–*H*), 7.01–7.40 (10H, m, Ar–H); δ_C (50 MHz, $CDCl_3$): 26.5, 26.6, 61.9, 76.0, 86.3, 96.4, 105.6, 114.0, 117.5, 124.3, 127.7, 128.5, 128.7, 129.0, 133.4, 136.9, 164.8. MS: *m*/*z* 368 (M+1).

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22. X-ray diffraction data for compound **12c**: single crystal X-ray structure determination of $C_{21}H_{21}NO_5$ was carried out using Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at room temperature. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.3° and with three different settings of φ (0°, 90°, and 180°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at −28°. The X-ray data collection was monitored by Bruker's SMART program (Bruker,

SMART, Version 5.0, Bruker AXS, Madison, WI, USA, 1998). All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs (Bruker, SAINT (V6.45a), Bruker AXS, Madison, WI, USA, 2004). SHELX-97 was used for structure solution and full matrix least squares refinement on F^2 (G. M. Sheldrick, SHELXS97, SHELXL97, University of Göttingen, Germany, 1997). Hydrogen atoms were included in the refinement as per the riding model. ORTEP diagram was generated using ORTEP-32 (M. N. Burnett, C. K. Johnson, ORTEPIII, Report ORNL-6895, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA, 1996). Crystal data for **12c**: $C_{21}H_{21}NO_5$; M=367.39; crystal size, 0.17×0.16×0.11 mm^3; T=297(2) K; crystal system, orthorhombic; space group, $P2_12_12_1$; a=5.7972(5), b=10.6478(10), c=30.579(3) Å; V=1887.6(3) Å^3; Z=4; F(000)=776; d calcd [g cm^{-3}]=1.293; μ [mm^{-1}]=0.093; absorption correction, multi-scan, T_{min}=0.9846; T_{max}=0.9898; 16,685 reflection collected, 3317 unique reflections, 2957 observed reflections, 247 refined parameters, R_1 [$I>2\sigma(I)$]=0.0352, wR_2=0.0769 (all data R=0.0411, $wR2$=0.0794); goodness of fit, 1.098; $\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})=0.130, −0.102. Crystallographic data of **12c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-646016. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK. The perspective view of the molecule is shown in Figure 4.

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