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1,3-Dipolar cycloaddition of nitrile oxides to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones: synthesis of enantiomerically pure spiro heterocycles

Raju Suresh Kumar,[a] Subbu Perumal,[a,*] Henri B. Kagan[b] and Regis Guillot[b]

[a]*Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India*
[b]*Institut de Chimie Moléculaire et des Matériaux d'Orsay (CNRS-UMR 8182), Université Paris-Sud, 91405 Orsay, France*

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Abstract—The 1,3-dipolar cycloaddition of (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones to nitrile oxides proceeds chemo-, regio-, and stereoselectively affording moderate yields of enantiomerically pure spiro heterocycles comprising piperidine and isoxazoline/dioxazole rings.

1. Introduction

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of five-membered heterocycles with multiple stereogenic centers.[1,2] Isoxazolines are versatile intermediates for the synthesis of a variety of bifunctional building blocks and bioactive compounds.[3–5] Isoxazolines, belonging to a class of unique pharmacophores, are found in many therapeutic agents such as GPII/IIIa inhibitors and human leukocyte elastase (HLE) inhibitors.[6] The piperidine ring systems are of great interest in the pharmaceutical industry as they exhibit a wide range of biological activities.[7]

The construction of chiral molecules is essential to explore new medicines and agrochemicals. It is obvious that the design of a specific chiral environment utilizing chiral auxiliaries provides a useful protocol to prepare optically active substances. α-Phenylethylamine is one of the most promising and less expensive chiral auxiliaries,[8] both enantiomers of which are readily available.

The biological activities of the isoxazoline and piperidine rings and our continued interest in the synthesis of novel heterocycles[9–13] prompted us to investigate the synthesis of enantiomerically pure spiro heterocycles comprising both piperidine and isoxazoline or dioxazole ring systems through the 1,3-dipolar cycloaddition of nitrile oxides to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **2** and we report the results in this paper. Further, it would also be of interest to unearth the factors that are underlying the stereoselectivity of these cycloadditions, as the dipolarophiles could exist in the form of diastereomeric conformations arising from ring flip and *N*-inversion. Recently, we have reported the 1,3-dipolar cycloaddition of nitrones to 3,5-bis(arylidene)-1-methylpiperidin-4-ones.[12] The present work constitutes the first investigation on the 1,3-dipolar cycloaddition of (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones.

2. Results and discussion

The (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone **1** was obtained by a literature procedure.[14] The (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **2** were synthesized in moderate yields (58–72%) through a solvent-free reaction of pyridinone **1** with aromatic aldehydes in the presence of pyrrolidine under microwave irradiation (Scheme 1). All the five (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **2** obtained as viscous liquids are new

* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

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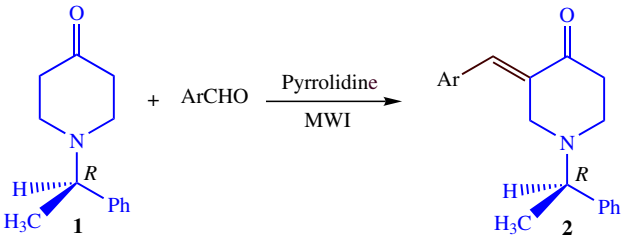


Comp.	Ar	Irradiation time (min.)	Yield (%)
2a	C_6H_5	3.5	58
2b	*p*-ClC_6H_4	3.0	65
2c	*p*-MeC_6H_4	3.5	68
2d	*o*-ClC_6H_4	3.0	72
2e	1-naphthyl	4.0	63

Scheme 1.

compounds and their structures are in good agreement with their ^1H, ^{13}C, and 2D NMR spectroscopic data (Fig. 1). All compounds of series **2** were obtained as viscous liquids and hence X-ray crystallographic studies could not be performed to unambiguously determine the configuration of the C=C bond. Energy minimization of **2a** employing AM1 calculations (Hyperchem software) suggests that the (*E*)-form is more stable than the (*Z*)-form as is evident from the heat of formation of (*E*)- and (*Z*)-forms, −4649.61 and −4645.98 kcal/mol, respectively. The stereochemistry of the cycloaddition products is also in accord with the (*E*)-form of **2** (vide infra).

The 1,3-dipolar cycloaddition of nitrile oxide, generated in situ from 4-chlorobenzohydroximoyl chloride and triethylamine[15] to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **2** (Scheme 2), afforded two spiroisoxazolines, **3** and **4**, in 52–56% and 8–10%, respectively. In the case of **2** with an *o*-chlorophenyl ring, dispiro compound, **5g** and **5h**, in 6% and 7% yields, respectively, were also obtained. Flash column chromatographic separation of the cycloadducts on silica gel using petroleum ether–ethyl acetate led to pure **3** and **5**. Cycloadduct **4** is always contaminated with small amounts of **3**, from which the isolation of **4** in a pure state proved difficult.

The predominant formation of **3** in all the reactions shows that the cycloaddition proceeds (i) chemoselectively, with the nitrile oxide preferring to react with the C=C and not with C=O bond of **2**, (ii) regioselectively, the oxygen of the nitrile oxide adding over the α-carbon of the C=C bond of **2**, and (iii) stereoselectively, affording only one of the stereoisomers of the isoxazoline (**3**) as the major product. The cycloadducts were characterized by ^1H, ^{13}C, and 2D NMR spectroscopic techniques (H,H-COSY, C,H-COSY, and HMBC). Selected HMBC correlations of **3b** are given in Figure 2. The ^1H and ^{13}C chemical shifts of **3b** and **4b**, assigned by straightforward considerations, are depicted in Figure 3. The structure and stereochemistry of **3** has been fully elucidated from an X-ray crystallographic study of a single crystal of **3b** (Fig. 4).

The ^1H and ^{13}C chemical shifts of **3b** and **4b** differ a little. This suggests that the structures **3** and **4** probably possess a mirror-image relationship, if one ignores the configuration of *N*-α-phenylethyl group (inclusive of which points to a diastereomeric relationship). The other possible structures for **4** with the oxygen of the isoxazoline ring oriented axially (denoted as **4b′** and **4b″**) are excluded on the basis that only small differences exist between the chemical shifts of **3b** and **4b**. For instance, the carbonyl chemical shift for structures **4b′** or **4b″** might probably be anticipated to differ significantly from that of **3b** (probably more upfield), due to the steric interaction between the benzylic proton and the carbonyl function in **4b′** or **4b″**, contrary to the almost identical chemical shift observed for the carbonyl carbons, 204.3 and 204.1 ppm of **3b** and **4b**, respectively.

A comparison of the chemical shifts of the 6-CH_2 and 8-CH_2 of **3b** and **4b** is noteworthy. The proton, H-8ax of **3b**, appears more upfield (2.75–2.87 ppm) than H-8ax (2.92–3.02 ppm) of **4b**, while the H-8eq of **3b** appears more downfield (2.49–2.67 ppm) than H-8eq (2.31–2.43 ppm) of **4b**. This can be explained as follows. All the three conformations of **3b**, viz. **3b**, **3b′**, and **3b″** depicted in Figure 5, are likely to suffer from steric interactions between the groups of α-phenylethyl group and the piperidone ring hydrogens, viz. methyl and H-8eq in **3b**, phenyl and H-8eq as well as methyl and H-6eq in **3b′** and methyl

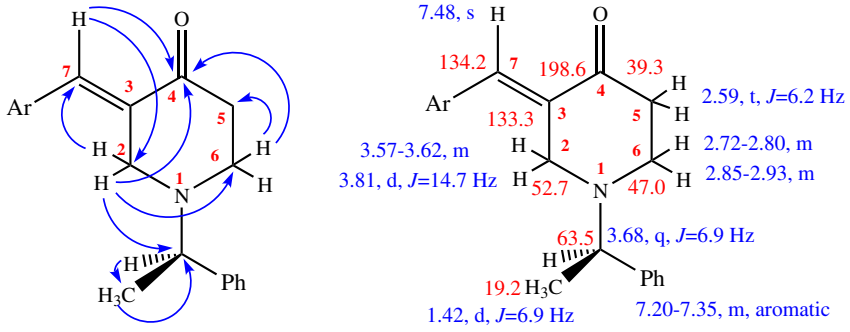
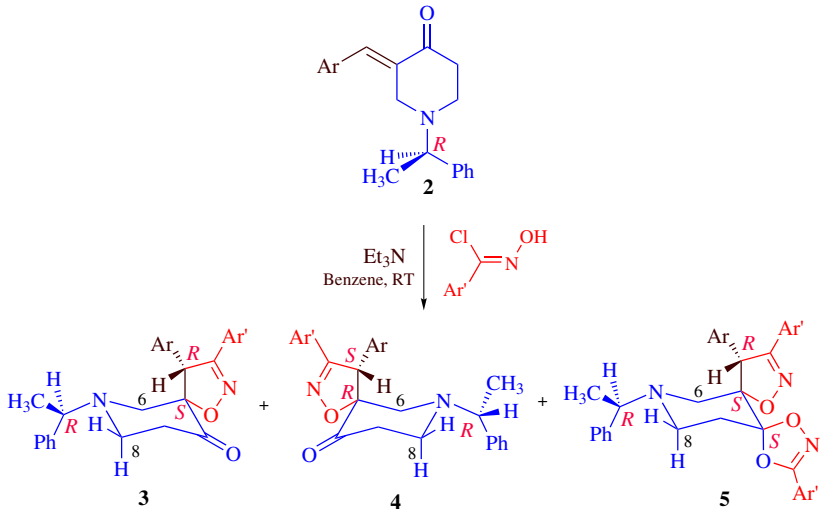


Figure 1. Selected HMBC correlations and ^1H and ^{13}C chemical shifts of **2b**.



Comp.	Ar	Ar'	3[a]	4[b]	5[a]
a	C_6H_5	C_6H_5	56	8	-
b	C_6H_5	*p*-ClC_6H_4	54	10	-
c	*p*-ClC_6H_4	C_6H_5	54	8	-
d	*p*-ClC_6H_4	*p*-ClC_6H_4	55	9	-
e	*p*-MeC_6H_4	C_6H_5	54	10	-
f	*p*-MeC_6H_4	*p*-ClC_6H_4	53	8	-
g	*o*-ClC_6H_4	C_6H_5	52	8	6
h	*o*-ClC_6H_4	*p*-ClC_6H_4	53	8	7
i	1-naphthyl	C_6H_5	54	10	-
j	1-naphthyl	*p*-ClC_6H_4	52	9	-

[a] Isolated yields of pure **3** and pure **5**.
[b] Yield from ^{1}H NMR signal intensities of **3** and **4** from the isolated **4** containing small amounts of **3**.

Scheme 2. Synthesis of spiroisoxazolines and spirodioxazoles.

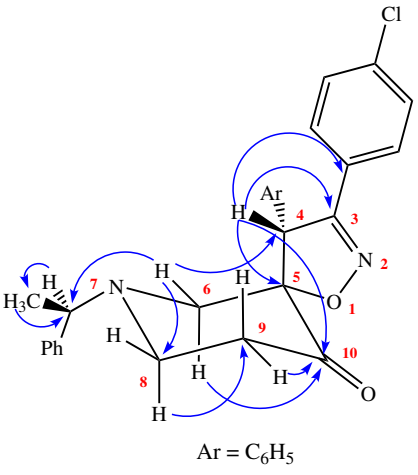


Figure 2. Selected HMBC correlations of **3b**.

with both H-8ax and H-6ax in **3b**″ diminishing the stability of all these conformations. The conformation, **3B** in Figure 6 with the π-plane of the phenyl ring moved close to H-8ax and the methyl moved away from the H-8eq relative to **3b** (Fig. 5) is likely to be the most stable conformation with minimum steric interaction. By similar considerations, the phenyl ring of the α-phenylethyl group in the most stable conformation of **4b**, viz. **4B** (Fig. 6), would be closer to H-6ax. The aryl ring of **3B** being proximate to H-8ax would shield it and deshield H-8eq relative to the corresponding protons in **4B**. Similarly, the proximity of the phenyl ring to H-6ax in **4B** would shield H-6ax (2.16 ppm) and deshield H-6eq (2.74 ppm) relative to the corresponding protons in **3B** (Fig. 6), which has chemical shift values of 2.37 ppm for H-6ax and 2.49–2.67 ppm for H-6eq. The above trends in the chemical shifts of **3b** and **4b** support the stereochemical relationship between **3** and **4**.

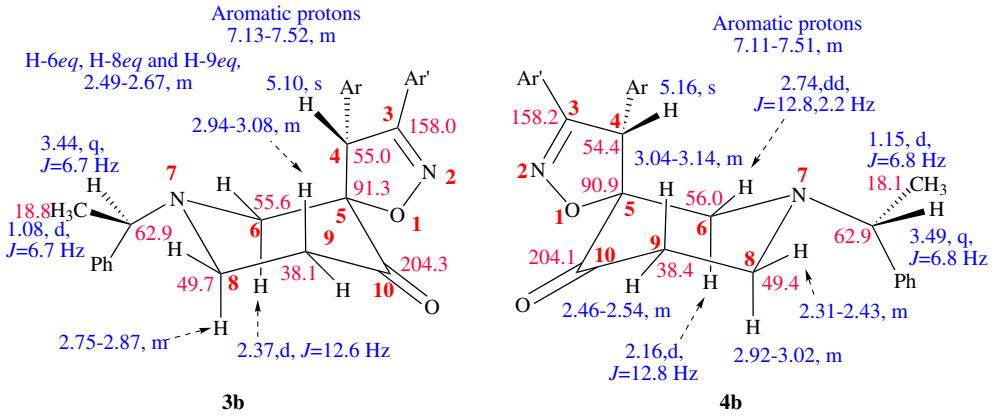


Figure 3. ^{1}H and ^{13}C chemical shifts of **3b** and **4b**.

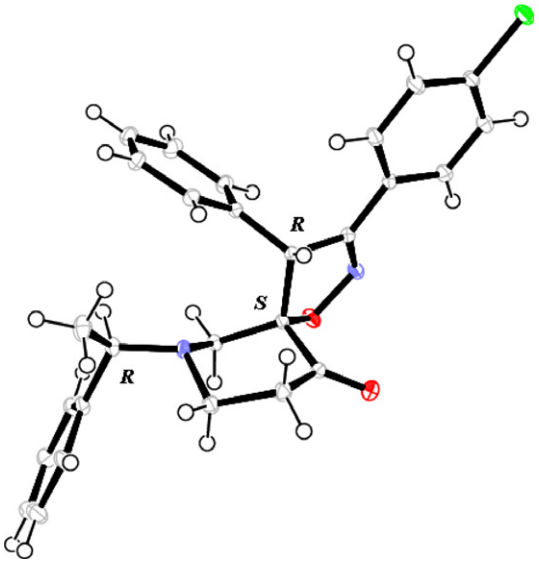


Figure 4. X-ray structure of **3b**.

The formation of **3b** and **4b** from the cycloaddition of nitrile oxide over **2** can be rationalized if one considers the conformational equilibrium of **2** arising from ring flip and *N*-inversion (Scheme 3), involving three conformational diastereomers **2A**, **2B**, and **2C**, each with different reactivity toward the cycloaddition. The reaction of the nitrile oxides from the bottom side of the general plane of **2A** and **2C** would explain the formation of products **3** and **4**, respectively. The reaction of **2B** could also lead to the formation of **4**, after *N*-inversion of **6** either after it is formed, or during the cycloaddition itself, although this reaction could be expected to be slow.

The formation of **3** and **4** in preference to **4b′** and **4b″** (Fig. 7) suggests that the transition states leading to **4b′** and **4b″** by attack of the dipole from the topside of **2A** and **2B** requires higher free energy of activation than those leading to **3b** and **4b**. This may probably be ascribed to (i) the repulsion between the nitrogen lone pair of **2A** or **2B** and the electron pairs of oxygen of the nitrile oxide, and (ii) the steric interaction between the benzylic hydrogen and the carbonyl group in the transition state leading to **4b′** and **4b″**. The formation of **4** as the minor product may presumably be ascribed to the possibly greater steric interaction between the aryl group at the 4-position of the isoxazoline with the methyl group of the α-phenylethyl in **4** as well as **6** than the interaction between the 4-aryl and hydrogen of the α-phenylethyl in **3**.

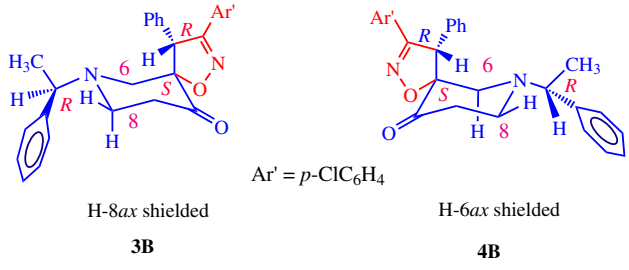


Figure 6. Most stable conformations of **3b** and **4b**.

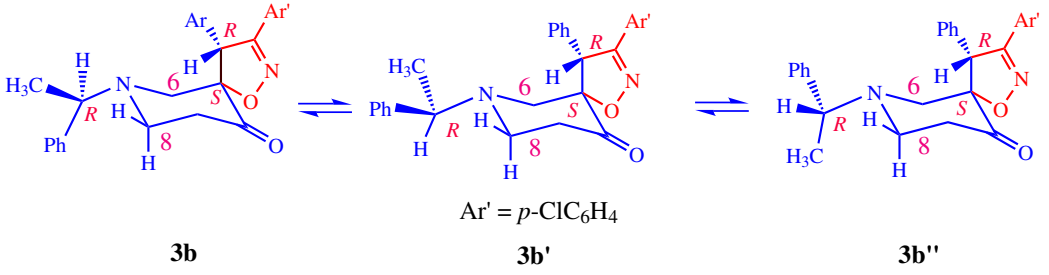
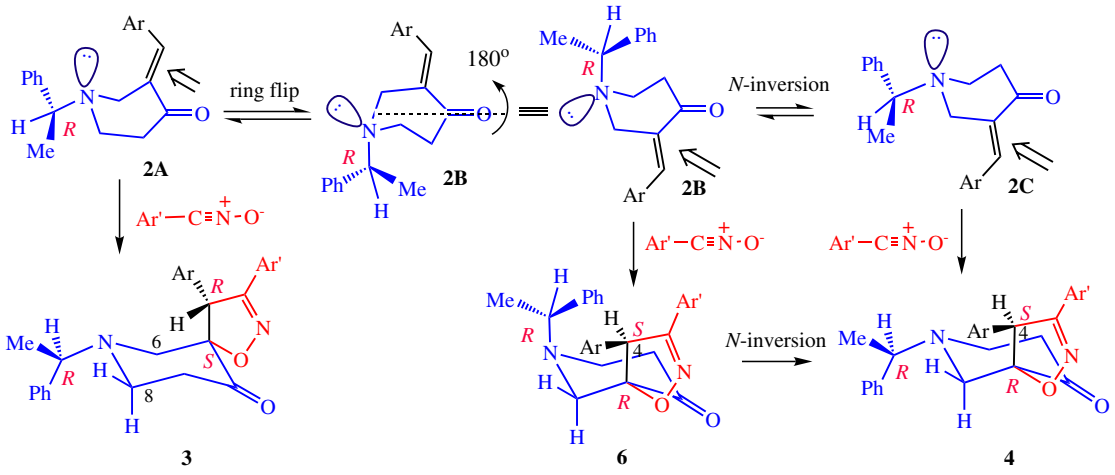


Figure 5. Conformational equilibrium of **3b**.



Scheme 3. Formation of monospiroheterocycles, **3** and **4**.

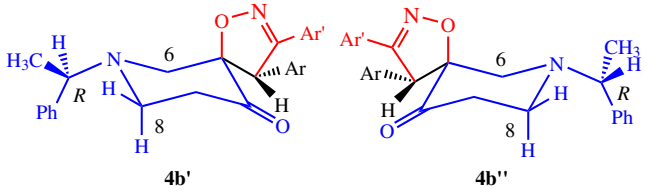


Figure 7.

The structure of **5** is found to be in accord with its NMR spectroscopic data. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **5h** assigned by straightforward considerations are given in Figure 8. The stereochemistry of **5h** has been fully elucidated from a single crystal X-ray study (Fig. 9). The structure of **5h** (Fig. 9) shows that the configuration at the stereocenters of isoxazoline is the same in **5h** and **3h**. This suggests that **5h** is presumably formed from further cycloaddition of the nitrile oxide over the C=O of **3h**. This is also confirmed by the formation of **5h** as the major product in a separate reaction of **3h** with nitrile oxide. The stereochemistry of **5h** shows that the nitrile oxide adds on the less hindered side of the C=O (viz. on the side of the oxygen of the isoxazoline) of **3h** leading to facial diastereoselectivity.

An explanation for the formation of **5**, viz. **5g** and **5h**, only in the case of nitrile oxide cycloaddition of **2d** with *o*-ClC_6H_4 is furnished below on the basis of electronic and steric interactions in the corresponding spiroisoxazolines, **3g** and **3h**, which undergo further cycloaddition to give

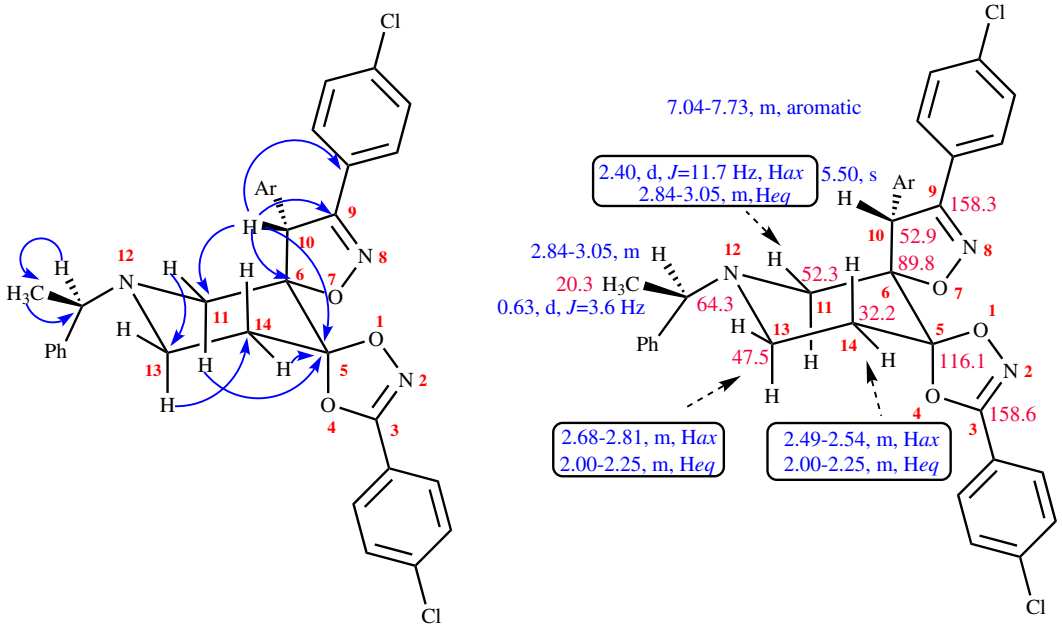


Figure 8. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **5h**.

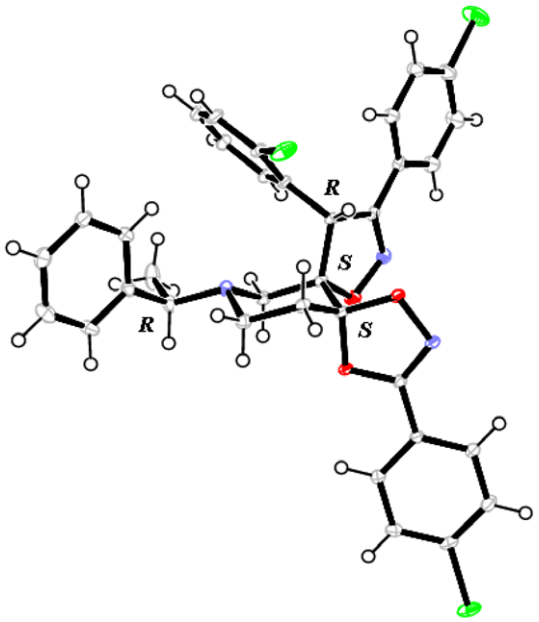


Figure 9. X-ray structure of **5h**.

5g and **5h**. The chlorine in *o*-ClC_6H_4 group of **3g** and **3h** can interact electronically with the proximal C=N–O functionality of the isoxazoline ring, while the *o*-chlorophenyl ring at C-10 and the aryl ring linked to the imino carbon (C-9) may interact sterically. These steric interactions between the aryl rings could alter their rotameric preferences in **3g** and **3h** relative to the other compounds of series **3** with *p*-substituted aryl at C-4. These electronic and steric interactions in **3g** and **3h** probably influence the electron distribution of the C=N–O functionality, which, in turn, can alter the electron distribution and polarity of the carbonyl through either spatial interactions or by the overlap of orbitals. These changes in the carbonyl originating from *o*-chlorophenyl presumably favor the second cycloaddition of **3g** and **3h** to afford **5g** and **5h**, respectively.

3. Conclusion

The present investigation describes a facile access to the enantiomerically pure novel dipolarophiles. The 1,3-dipolar cycloaddition of these dipolarophiles with nitrile oxides occurs chemo-, regio-, and stereoselectively to provide enantiomerically pure spiro heterocycles containing nitrogen and oxygen. The synthetic potential of the cycloaddition of the chiral dipolarophiles, described in this work, with other 1,3-dipoles is being currently explored in our research group.

4. Experimental

4.1. General methods

Melting points were taken using open capillary tubes and are uncorrected. ^1H, ^{13}C, and two-dimensional NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and $CHCl_3$ in case of liquids). The single crystal X-ray data set for **3b** and **5h** was collected on Bruker Kappa X8 APPEX II diffractometer with Mo K_α ($\lambda = 0.71073$ Å) radiation. Scan range was $2.22° \leqslant \theta \leqslant 33.00°$. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser. Column chromatography was performed on silica gel (230–400 mesh) using petroleum ether–ethyl acetate as eluent. Optical rotation values were measured using an autopol IV automatic polarimeter at sodium D line at 25 °C.

4.2. Preparation of 1-[(*R*)-1-phenylethyl]-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones 2a–e

4.2.1. General procedure. A mixture of **1** (1 mmol) and pyrrolidine (1 mmol) was mixed well in a semi-micro-boiling tube and irradiated for 0.5 min at maximum power level (600 W) in a microwave oven. Then aromatic aldehyde (1 mmol) is added to the mixture and again irradiated for appropriate time (2.5–3.5 min) at the same power level. The progress of the reaction was monitored intermittently after every 1 minute of irradiation by thin layer chromatography with petroleum ether–ethyl acetate (4:1 v/v mixture) as eluent. After completion of the reaction as evident from TLC, the resulting mixture is extracted with CH_2Cl_2 and subjected to column chromatography to obtain **2**.

4.2.2. 1-[(*R*)-1-Phenylethyl]-3-[(*E*)-phenylmethylidene]tetrahydro-4(1*H*)-pyridinone 2a. Obtained as a viscous liquid; $[\alpha]_D = +27.4$ (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): 1679, 1643, 1594, 1448, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, $J = 6.6$ Hz, CH_3), 2.59 (t, 2H, $J = 6.2$ Hz, H-5a and H-5b), 2.69–2.78 (m, 1H, H-6a), 2.85–2.93 (m, 1H, H-6b), 3.62–3.69 (m, 2H, H-2a and CH), 3.90 (d, 1H, $J = 15.0$ Hz, H-2b), 7.22–7.41 (m, 10H, aromatic), 7.56 (s, 1H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 39.3 (C-5), 46.9 (C-6), 52.8 (C-2), 63.5 (CH), 127.1, 127.3, 128.3, 128.4, 128.9, 130.3, 133.6 (C-3), 134.8, 135.6, 143.0 (aromatic), 198.8 (C-4). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.40; H, 7.32; N, 4.76.

4.2.3. 3-[(*E*)-(4-Chlorophenyl)methylidene]-1-[(*R*)-1-phenylethyl]tetrahydro-4(1*H*)-pyridinone 2b. Obtained as a viscous liquid; $[\alpha]_D = +19.3$ (*c* 0.21, $CHCl_3$); IR ($CHCl_3$): 1675, 1641, 1592, 1490, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, $J = 6.9$ Hz, CH_3), 2.59 (t, 2H, $J = 6.2$ Hz, H-5a and H-5b), 2.72–2.80 (m, 1H, H-6a), 2.85–2.93 (m, 1H, H-6b), 3.57–3.62 (m, 1H, H-2a), 3.68 (q, 1H, $J = 6.9$ Hz, CH), 3.81 (d, 1H, $J = 14.7$ Hz, H-2b), 7.20–7.35 (m, 9H, aromatic), 7.48 (s, 1H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 39.3 (C-5), 47.0 (C-6), 52.7 (C-2), 63.5 (CH), 127.2, 127.3, 128.4, 128.7, 131.5, 133.3 (C-3), 134.1, 134.2, 134.9, 142.9 (aromatic), 198.6 (C-4). Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30. Found: C, 73.76; H, 6.15; N, 4.34.

4.2.4. 3-[(*E*)-(4-Methylphenyl)methylidene]-1-[(*R*)-1-phenylethyl]tetrahydro-4(1*H*)-pyridinone 2c. Obtained as a viscous liquid; $[\alpha]_D = +42.6$ (*c* 0.19, $CHCl_3$); IR ($CHCl_3$): 1678, 1647, 1597, 1490, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, $J = 6.8$ Hz, CH_3), 2.37 (s, 3H, CH_3), 2.58 (t, 2H, $J = 6.0$ Hz, H-5a and H-5b), 2.67–2.76 (m, 1H, H-6a), 2.84–2.92 (m, 1H, H-6b), 3.61–3.63 (m, 1H, H-2a), 3.66 (q, 1H, $J = 6.8$ Hz, CH), 3.91 (d, 1H, $J = 14.7$ Hz, H-2b), 7.17–7.34 (m, 9H, aromatic), 7.54 (s, 1H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8 (CH_3), 21.8 (CH_3), 39.8 (C-5), 47.5 (C-6), 53.4 (C-2), 64.1 (CH), 127.6, 127.8, 128.8, 129.7, 131.0, 132.6, 133.2 (C-3), 136.3, 139.7, 143.6 (aromatic), 199.2 (C-4). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.63; H, 7.54; N, 4.62.

4.2.5. 3-[(*E*)-(2-Chlorophenyl)methylidene]-1-[(*R*)-1-phenylethyl]tetrahydro-4(1*H*)-pyridinone 2d. Obtained as a viscous liquid; $[\alpha]_D = +31.9$ (*c* 0.16, $CHCl_3$); IR ($CHCl_3$): 1671, 1654, 1590, 1474, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, 3H, $J = 7.0$ Hz, CH_3), 2.61 (t, 2H, $J = 6.0$ Hz, H-5a and H-5b), 2.75–2.83 (m, 1H, H-6a), 2.90–2.97 (m, 1H, H-6b), 3.50 (d, 1H, $J = 15.2$ Hz, H-2a), 3.60–3.68 (m, 1H, CH), 3.83 (d, 1H, $J = 15.2$ Hz, H-2b), 7.04–7.43 (m, 9H, aromatic), 7.66 (s, 1H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (CH_3), 39.3 (C-5), 47.2 (C-6), 52.1 (C-2), 62.9 (CH), 126.3, 127.2, 127.3, 128.3, 129.8, 130.1, 132.3, 133.3 (C-3), 134.7, 135.3, 143.0 (aromatic), 198.8 (C-4). Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30. Found: C, 73.67; H, 6.23; N, 4.27.

4.2.6. 3-[(*E*)-1-Naphthylmethylidene]-1-[(*R*)-1-phenylethyl]-tetrahydro-4(1*H*)-pyridinone 2e. Obtained as a viscous liquid; $[\alpha]_D = +31.0$ (*c* 0.20, $CHCl_3$); IR ($CHCl_3$): 1684, 1656, 1580, 1440, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, 3H, $J = 6.6$ Hz, CH_3), 2.64 (t, 2H, $J = 6.0$ Hz, H-5a and H-5b), 2.72–2.77 (m, 1H, H-6a), 2.88–2.94 (m, 1H, H-6b), 3.51 (d, 1H, $J = 14.6$ Hz, H-2a), 3.58 (q, 1H, $J = 6.6$ Hz, CH), 3.73 (d, 1H, $J = 14.6$ Hz, H-2b), 7.22–7.99 (m, 12H, aromatic), 8.13 (s, 1H, CHAr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (CH_3), 39.4 (C-5), 47.3 (C-6), 52.4 (C-2), 63.1 (CH), 124.6, 124.9, 126.2, 126.5, 126.7, 127.1, 127.3, 128.2, 128.3, 128.5, 129.2, 131.9, 133.4 (C-3), 133.6, 135.5, 142.8 (aromatic), 198.9 (C-4). Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.45; H, 6.83; N, 4.06.

4.3. Cycloaddition of benzohydroximoyl chloride with 1-[(*R*)-1-phenylethyl]-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones

4.3.1. General procedure. [(*R*)-1-Phenylethyl]-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone **2** (1 mmol) was dissolved in benzene (15 mL). To this solution, benzohydroximoyl chloride (1.5 mmol) was added and the mixture stirred at room temperature. Triethylamine (1.5 mmol) was dissolved in benzene (10 mL) and was added dropwise to the above mixture and stirring continued for 9–12 h. The reaction mixture was filtered to remove the triethylamine hydrochloride and the solvent was evaporated in vacuo. The residue was subjected to flash column chromatography on silica gel (10:1 petroleum ether–ethyl acetate).

4.3.2. (4*R*,5*S*)-3,4-Diphenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3a. Obtained as colorless crystals; mp = 168–169 °C; $[\alpha]_D = -232.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1724, 1490, 1448, 1332, 1187, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, 3H, $J = 6.9$ Hz, CH_3), 2.40 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.53–2.64 (m, 3H, H-6eq, H-8eq and H-9eq), 2.74–2.83 (m, 1H, H-8ax), 2.95–3.06 (m, 1H, H-9ax), 3.44 (q, 1H, $J = 6.9$ Hz, CH), 5.13 (s, 1H, H-4), 7.14–7.59 (m, 15H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8 (CH_3), 38.1 (C-9), 49.7 (C-8), 55.3 (C-4), 55.6 (C-6), 62.9 (CH), 91.2 (C-5), 127.1, 127.2, 127.4, 128.1, 128.2, 128.3, 128.5, 128.9, 130.0, 132.9, 142.5 (aromatic), 158.9 (C-3), 204.6 (C-10). Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.96; H, 6.42; N, 6.79.

4.3.3. (4*S*,5*R*)-3,4-Diphenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4a.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1725, 1580, 1459, 1338, 1120, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, 3H, $J = 6.9$ Hz, CH_3), 2.18 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.46–2.64 (m, 3H, H-6eq, H-8eq, and H-9eq), 2.71–2.82 (m, 1H, H-8ax), 3.07–3.14 (m, 1H, H-9ax), 3.48 (q, 1H, $J = 6.9$ Hz, CH), 5.19 (s, 1H, H-4), 7.14–7.59 (m, 15H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH_3), 38.4 (C-9), 49.5 (C-8), 54.5 (C-4), 56.0 (C-6), 62.9 (CH), 90.8 (C-5), 127.2, 127.4, 127.5, 128.1, 128.2, 128.4, 128.5, 128.8, 128.9, 130.0, 133.0, 141.6 (aromatic), 159.1 (C-3), 204.3 (C-10).

4.3.4. (4*R*,5*S*)-3-(4-Chlorophenyl)-4-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3b. Obtained as colorless crystals; mp = 189–190 °C; $[\alpha]_D = -256.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1772, 1490, 1452, 1330, 1191, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, 3H, $J = 6.7$ Hz, CH_3), 2.37 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.49–2.67 (m, 3H, H-6eq, H-8eq, and H-9eq), 2.75–2.87 (m, 1H, H-8ax), 2.94–3.08 (m, 1H, H-9ax), 3.44 (q, 1H, $J = 6.7$ Hz, CH), 5.10 (s, 1H, H-4), 7.13–7.52 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.8 (CH_3), 38.1 (C-9), 49.7 (C-8), 55.0 (C-4), 55.6 (C-6), 62.9 (CH), 91.3 (C-5), 126.9, 127.1, 127.2, 128.2, 128.3, 128.6, 128.8, 129.0, 132.7, 136.0, 142.4 (aromatic), 158.0 (C-3), 204.3 (C-10). Anal. Calcd for $C_{27}H_{25}ClN_2O_2$: C, 72.88; H, 5.66; N, 6.30. Found: C, 72.83; H, 5.62; N, 6.34.

4.3.5. (4*S*,5*R*)-3-(4-Chlorophenyl)-4-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4b.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1722, 1580, 1459, 1340, 1139, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 6.8$ Hz, CH_3), 2.16 (d, 1H, $J = 12.8$ Hz, H-6ax), 2.31–2.43 (m, 1H, H-8eq), 2.46–2.54 (m, 1H, H-9eq), 2.74 (dd, 1H, $J = 12.8$, 2.2 Hz, H-6eq), 2.92–3.02 (m, 1H, H-8ax), 3.04–3.14 (m, 1H, H-9ax), 3.49 (q, 1H, $J = 6.8$ Hz, CH), 5.16 (s, 1H, H-4), 7.11–7.51 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH_3), 38.4 (C-9), 49.4 (C-8), 54.4 (C-4), 56.0 (C-6), 62.9 (CH), 90.9 (C-5), 126.9, 127.1, 127.2, 127.5, 128.2, 128.3, 128.7, 128.8, 129.0, 132.7, 136.0, 141.5 (aromatic), 158.2 (C-3), 204.1 (C-10).

4.3.6. (4*R*,5*S*)-4-(4-Chlorophenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3c. Obtained as colorless crystals; mp = 96–97 °C; $[\alpha]_D = -182.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1779, 1498, 1450, 1342, 1170, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 3H, $J = 6.8$ Hz, CH_3), 2.33 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.51–2.62 (m, 3H, H-6eq, H-8eq and H-9eq), 2.82–2.87 (m, 1H, H-8ax), 2.96–3.06 (m, 1H, H-9ax), 3.45 (q, 1H, $J = 6.8$ Hz, CH), 5.14 (s, 1H, H-4), 7.19–7.47 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (CH_3), 37.9 (C-9), 49.5 (C-8), 54.2 (C-4), 55.7 (C-6), 62.9 (CH), 90.9 (C-5), 127.0, 127.1, 127.2, 127.3, 127.9, 128.1, 128.5, 128.9, 130.1, 131.5, 134.0, 142.2 (aromatic), 158.6 (C-3), 204.1 (C-10). Anal. Calcd for $C_{27}H_{25}ClN_2O_2$: C, 72.88; H, 5.66; N, 6.30. Found: C, 72.91; H, 5.62; N, 6.36.

4.3.7. (4*S*,5*R*)-4-(4-Chlorophenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4c.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1729, 1589, 1446, 1354, 1142, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, 3H, $J = 6.8$ Hz, CH_3), 2.17 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.38–2.49 (m, 1H, H-8eq), 2.50–2.58 (m, 1H, H-9eq), 2.72 (dd, 1H, $J = 12.6$, 1.8 Hz, H-6eq), 2.95–2.99 (m, 1H, H-8ax), 3.03–3.13 (m, 1H, H-9ax), 3.51 (q, 1H, $J = 6.8$ Hz, CH), 5.18 (s, 1H, H-4), 7.11–7.56 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH_3), 38.3 (C-9), 49.5 (C-8), 53.8 (C-4), 55.9 (C-6), 62.9 (CH), 90.6 (C-5), 127.2, 127.3, 127.4, 127.9, 128.2, 128.6, 129.2, 130.2, 130.5, 131.6, 134.1, 141.5 (aromatic), 158.9 (C-3), 204.0 (C-10).

4.3.8. (4*R*,5*S*)-3,4-Bis(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3d. Obtained as colorless crystals; mp = 101–102 °C; $[\alpha]_D = -162.5$ (*c* 0.20, $CHCl_3$); IR (KBr): 1769, 1490, 1445, 1350, 1184, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 6.9$ Hz, CH_3), 2.27 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.50–2.63 (m, 3H, H-6eq, H-8eq and H-9eq), 2.87–2.92 (m, 1H, H-8ax), 2.99–3.10 (m, 1H, H-9ax), 3.46 (q, 1H, $J = 6.9$ Hz, CH), 5.11 (s, 1H, H-4), 7.06–7.49 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (CH_3), 38.1 (C-9), 49.6 (C-8), 54.0 (C-4), 55.9 (C-6), 62.9 (CH), 91.1 (C-5), 126.5, 127.2, 128.3, 128.6, 128.9, 129.2, 130.4, 131.2, 134.3, 136.2, 142.2 (aromatic), 157.8 (C-3), 204.0 (C-10). Anal. Calcd for $C_{27}H_{24}Cl_2N_2O_2$: C, 67.65; H, 5.05; N, 5.84. Found: C, 67.60; H, 5.09; N, 5.81.

4.3.9. (4*S*,5*R*)-3,4-Bis(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4d.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1732, 1578, 1451, 1362, 1153, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, 3H, $J = 6.9$ Hz, CH_3), 2.15 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.39–2.49 (m, 1H, H-8eq), 2.50–2.63 (m, 1H, H-9eq), 2.72 (dd, 1H, $J = 12.9$, 1.8 Hz, H-6eq), 2.99–3.04 (m, 1H, H-8ax), 3.08–3.14 (m, 1H, H-9ax), 3.52 (q, 1H, $J = 6.9$ Hz, CH), 5.15 (s, 1H, H-4), 7.15–7.49 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2 (CH_3), 38.3 (C-9), 49.5 (C-8), 53.7 (C-4), 56.0 (C-6), 62.9 (CH), 90.9 (C-5), 126.5, 127.2, 127.4, 128.2, 128.6, 128.9, 129.3, 131.3, 134.4, 136.3, 141.5 (aromatic), 158.0 (C-3), 203.8 (C-10).

4.3.10. (4*R*,5*S*)-4-(4-Methylphenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3e. Obtained as colorless crystals; mp = 147–148 °C; $[\alpha]_D = -212.5$ (*c* 0.20, $CHCl_3$); IR (KBr): 1775, 1496, 1452, 1360, 1192, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, 3H, $J = 6.6$ Hz, CH_3), 2.30 (s, 1H, CH_3), 2.43 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.48–2.64 (m, 3H, H-6eq, H-8eq and H-9eq), 2.73–2.81 (m, 1H, H-8ax), 2.90–3.03 (m, 1H, H-9ax), 3.45 (q, 1H, $J = 6.6$ Hz, CH), 5.09 (s, 1H, H-4), 7.14–7.52 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 21.1 (CH_3), 38.0 (C-9), 49.6 (C-8), 54.9 (C-4), 55.6 (C-6), 62.8 (CH), 91.1 (C-5), 127.0, 127.2, 127.3, 128.1, 128.2, 128.3, 128.4, 129.5, 129.8, 129.9, 137.8, 142.7 (aromatic), 159.0 (C-3), 204.6 (C-10). Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.26; H, 6.69; N, 6.53.

4.3.11. (4*S*,5*R*)-4-(4-Methylphenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4e.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1721, 1572, 1456, 1369, 1146, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 6.6$ Hz, CH_3), 2.20 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.31 (s, 1H, CH_3), 2.37–2.48 (m, 1H, H-8eq), 2.52–2.64 (m, 1H, H-9eq), 2.78 (dd, 1H, $J = 12.6$, 1.8 Hz, H-6eq), 2.90–2.99 (m, 1H, H-8ax), 3.02–3.11 (m, 1H, H-9ax), 3.48 (q, 1H, $J = 6.6$ Hz, CH), 5.15 (s, 1H, H-4), 7.09–7.59 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (CH_3), 21.1 (CH_3), 38.4 (C-9), 49.6 (C-8), 54.3 (C-4), 56.0 (C-6), 62.9 (CH), 90.7 (C-5), 127.1, 127.2, 127.4, 127.5, 128.1, 128.2, 128.4, 129.6, 129.8, 129.9, 137.8, 141.8 (aromatic), 159.2 (C-3), 204.4 (C-10).

4.3.12. (4*R*,5*S*)-3-(4-Chlorophenyl)-4-(4-methylphenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3f. Obtained as colorless crystals; mp = 156–157 °C; $[\alpha]_D = -197.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1770, 1490, 1459, 1348, 1199, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, 3H, $J = 6.3$ Hz, CH_3), 2.31 (s, 1H, CH_3), 2.41 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.53–2.58 (m, 2H, H-8eq and H-9eq), 2.62 (d, 1H, $J = 12.9$ Hz, H-6eq), 2.75–2.82 (m, 1H, H-8ax), 2.93–3.00 (m, 1H, H-9ax), 3.45 (q, 1H, $J = 6.3$ Hz, CH), 5.07 (s, 1H, H-4), 7.10–7.52 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (CH_3), 21.1 (CH_3), 38.0 (C-9), 49.5 (C-8), 54.7 (C-4), 55.5 (C-6), 62.8 (CH), 91.3 (C-5), 126.8, 127.0, 127.2, 127.4, 128.0, 128.1, 128.6, 128.7, 129.4, 129.6, 138.0, 142.5 (aromatic), 158.0 (C-3), 204.4 (C-10). Anal. Calcd for $C_{28}H_{27}ClN_2O_2$: C, 73.27; H, 5.93; N, 6.10. Found: C, 73.31; H, 5.90; N, 6.05.

4.3.13. (4*S*,5*R*)-3-(4-Chlorophenyl)-4-(4-methylphenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4f.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1728, 1580, 1449, 1353, 1140, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 6.6$ Hz, CH_3), 2.20 (d, 1H, $J = 12.6$ Hz, H-6ax), 2.31 (s, 1H, CH_3), 2.53–2.58 (m, 3H, H-6eq, H-8eq, and H-9eq), 2.75–2.82 (m, 1H, H-8ax), 3.02–3.10 (m, 1H, H-9ax), 3.47 (q, 1H, $J = 6.6$ Hz, CH), 5.12 (s, 1H, H-4), 7.10–7.52 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0 (CH_3), 21.1 (CH_3), 38.3 (C-9), 49.4 (C-8), 54.1 (C-4), 55.8 (C-6), 62.8 (CH), 90.8 (C-5), 126.8, 127.0, 127.1, 127.3, 128.0, 128.1, 128.5,

128.7, 129.4, 129.5, 135.8, 141.7 (aromatic), 158.2 (C-3), 204.1 (C-10).

4.3.14. (4*R*,5*S*)-4-(2-Chlorophenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3g. Obtained as colorless crystals; mp = 165–166 °C; $[\alpha]_D = -242.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1768, 1484, 1452, 1360, 1190, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, 3H, $J = 6.9$ Hz, CH_3), 2.38 (d, 1H, $J = 12.3$ Hz, H-6ax), 2.48–2.56 (m, 1H, H-8eq), 2.62–2.65 (m, 1H, H-9eq), 2.67 (d, 1H, $J = 12.3$ Hz, H-6eq), 2.87–2.92 (m, 1H, H-8ax), 2.95–3.07 (m, 1H, H-9ax) 3.50 (q, 1H, $J = 6.9$ Hz, CH), 5.78 (s, 1H, H-4), 6.99–7.61 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0 (CH_3), 38.2 (C-9), 49.9 (C-8), 50.9 (C-4), 54.7 (C-6), 63.0 (CH), 90.7 (C-5), 127.2, 127.3, 127.5, 127.9, 128.2, 128.7, 129.5, 130.0, 130.2, 130.7, 131.3, 134.0, 141.6 (aromatic), 159.2 (C-3), 203.4 (C-10). Anal. Calcd for $C_{27}H_{25}ClN_2O_2$: C, 72.88; H, 5.66; N, 6.30. Found: C, 72.85; H, 5.62; N, 6.27.

4.3.15. (4*S*,5*R*)-4-(2-Chlorophenyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4g.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1727, 1587, 1454, 1346, 1128, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (d, 3H, $J = 6.6$ Hz, CH_3), 2.53 (d, 1H, $J = 12.2$ Hz, H-6ax), 2.59–2.65 (m, 2H, H-8eq and H-9eq), 2.70 (d, 1H, $J = 12.2$ Hz, H-6eq), 2.79–2.86 (m, 1H, H-8ax), 2.89–3.04 (m, 1H, H-9ax), 3.29 (q, 1H, $J = 6.6$ Hz, CH), 5.68 (s, 1H, H-4), 6.95–7.57 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (CH_3), 37.9 (C-9), 49.8 (C-8), 51.9 (C-4), 55.1 (C-6), 63.3 (CH), 91.1 (C-5), 127.0, 127.1, 127.2, 127.5, 127.9, 128.3, 128.6, 129.5, 129.9, 130.2, 130.6, 131.3, 134.2, 142.8 (aromatic), 158.9 (C-3), 203.9 (C-10).

4.3.16. (4*R*,5*S*,10*S*)-10-(2-Chlorophenyl)-3,9-diphenyl-12-[(*R*)-1-phenylethyl]-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene 5g. Obtained as colorless crystals; mp = 172–173 °C; $[\alpha]_D = -62.0$ (*c* 0.10, $CHCl_3$); IR (KBr): 3018, 2400, 1521, 1417, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.59 (d, 3H, $J = 6.5$ Hz, CH_3), 2.17–2.20 (m, 1H, H-14eq), 2.60–2.71 (m, 3H, H-11ax, H-13eq, and H-14ax), 2.98 (q, 1H, $J = 6.5$ Hz, CH), 3.17 (d, 1H, H-13ax, $J = 10.2$ Hz), 3.69 (d, 1H, H-11eq, $J = 12.6$ Hz), 5.57 (s, 1H, H-10), 6.84–7.84 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 32.2 (C-14), 49.7 (C-13), 52.4 (C-11), 52.9 (C-10), 64.5 (CH), 89.8 (C-6), 115.2 (C-5), 122.9, 127.1, 127.2, 127.3, 128.2, 128.3, 128.5, 128.6, 128.7, 129.2, 129.7, 130.0, 130.8, 131.2, 133.5, 133.8, 135.2, 143.6 (aromatic), 158.5 (C-9), 160.2 (C-3). Anal. Calcd for $C_{34}H_{30}ClN_3O_3$: C, 72.40; H, 5.36; N, 7.45. Found: C, 72.37; H, 5.32; N, 7.49.

4.3.17. (4*R*,5*S*)-4-(2-Chlorophenyl)-3-(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3h. Obtained as colorless crystals; mp = 152–153 °C; $[\alpha]_D = -210.5$ (*c* 0.20, $CHCl_3$); IR (KBr): 1775, 1474, 1446, 1372, 1182, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, 3H, $J = 6.9$ Hz, CH_3), 2.37 (d, 1H, $J = 12.5$ Hz, H-6ax), 2.49–2.55 (m, 1H, H-8eq), 2.56–2.62 (m, 1H, H-9eq), 2.67 (d, 1H, $J = 12.5$ Hz, H-6eq), 2.85–2.90 (m, 1H, H-8ax), 2.92–3.03 (m, 1H, H-9ax), 3.50 (q, 1H, $J = 6.9$ Hz, CH), 5.74 (s, 1H, H-4), 7.14–7.55 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 (CH_3), 38.2 (C-9), 49.8 (C-8), 50.7 (C-4), 54.5 (C-6), 62.9 (CH), 90.8 (C-5), 126.5, 127.1, 127.4, 127.9, 128.1, 128.5, 128.9, 129.0, 130.1, 130.5, 130.9, 134.0, 136.2, 143.6 (aromatic), 158.2 (C-3), 203.2 (C-10). Anal. Calcd for $C_{27}H_{24}Cl_2N_2O_2$: C, 67.65; H, 5.05; N, 5.84. Found: C, 67.61; H, 5.02; N, 5.89.

4.3.18. (4*S*,5*R*)-4-(2-Chlorophenyl)-3-(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4h.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1720, 1572, 1440, 1359, 1148, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (d, 3H, $J = 6.6$ Hz, CH_3), 2.52 (d, 1H, $J = 12.5$ Hz, H-6ax), 2.62–2.63 (m, 2H, H-8eq and H-9eq), 2.69 (d, 1H, $J = 12.5$ Hz, H-6eq), 2.74–2.82 (m, 2H, H-8ax and H-9ax), 3.28 (q, 1H, $J = 6.6$ Hz, CH), 5.64 (s, 1H, H-4), 6.97–7.72 (m, 13H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (CH_3), 37.9 (C-9), 49.7 (C-8), 51.8 (C-4), 55.1 (C-6), 63.3 (CH), 91.3 (C-5), 126.4, 127.1, 127.5, 127.9, 128.3, 128.5, 129.0, 129.7, 130.0, 130.5, 131.0, 134.1, 136.3, 142.7 (aromatic), 158.0 (C-3), 203.8 (C-10).

4.3.19. (4*R*,5*S*,10*S*)-10-(2-Chlorophenyl)-3,9-bis(4-chlorophenyl)-12-[(*R*)-1-phenylethyl]-1,4,7-trioxa-2,8,12-triazadispiro[4.0.4.4]tetradeca-2,8-diene 5h. Obtained as colorless crystals; mp = 181–182 °C; $[\alpha]_D = -50.0$ (*c* 0.10, $CHCl_3$); IR (KBr): 3012, 2412, 1518, 1424, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.63 (d, 3H, $J = 3.6$ Hz, CH_3), 2.00–2.25 (m, 2H, H-13eq and H-14eq), 2.40 (d, 1H, $J = 11.7$ Hz, H-11ax), 2.49–2.54 (m, 1H, H-14ax), 2.68–2.81 (m, 1H, H-13ax), 2.84–3.05 (m, 2H, CH and H-11eq), 5.50 (s, 1H, H-10), 7.04–7.73 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (CH_3), 32.2 (C-14), 47.5 (C-13), 52.3 (C-11), 52.9 (C-10), 64.3 (CH), 89.8 (C-6), 116.1 (C-5), 121.2, 126.6, 127.0, 127.3, 128.2, 128.3, 128.5, 128.8, 128.9, 129.4, 129.9, 130.7, 132.1, 134.8, 136.0, 137.6, 143.7 (aromatic), 158.3 (C-9), 158.6 (C-3). Anal. Calcd for $C_{34}H_{28}Cl_3N_3O_3$: C, 64.52; H, 4.46; N, 6.64. Found: C, 64.55; H, 4.49; N, 6.59.

4.3.20. (4*R*,5*S*)-4-(1-Naphthyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3i. Obtained as colorless crystals; mp = 138–139 °C; $[\alpha]_D = -187.5$ (*c* 0.20, $CHCl_3$); IR (KBr): 1769, 1480, 1458, 1384, 1164, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 3H, $J = 6.6$ Hz, CH_3), 1.94 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.15–2.27 (m, 1H, H-8eq), 2.45–2.51 (m, 1H, H-9eq), 2.78 (dd, 1H, $J = 12.9$, 2.4 Hz, H-6eq), 2.98–3.02 (m, 1H, H-8ax), 3.17–3.22 (m, 1H, H-9ax), 3.26 (q, 1H, $J = 6.6$ Hz, CH), 6.27 (s, 1H, H-4), 6.96–8.19 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 38.6 (C-9), 48.4 (C-4), 49.8 (C-8), 56.2 (C-6), 62.8 (CH), 91.0 (C-5), 122.8, 125.4, 125.9, 126.9, 127.1, 127.2, 127.4, 127.9, 128.0, 128.3, 128.5, 128.6, 129.1, 129.2, 129.9, 131.7, 134.0, 141.9 (aromatic), 159.4 (C-3), 204.5 (C-10). Anal. Calcd for $C_{31}H_{28}N_2O_2$: C, 80.84; H, 6.13; N, 6.08. Found: C, 80.81; H, 6.10; N, 6.11.

4.3.21. (4*S*,5*R*)-4-(1-Naphthyl)-3-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4i.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1722, 1581, 1452, 1348, 1157, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):

δ 0.87 (d, 3H, $J = 6.8$ Hz, CH_3), 2.24 (d, 1H, $J = 12.8$ Hz, H-6ax), 2.37–2.45 (m, 1H, H-8eq), 2.52–2.59 (m, 1H, H-9eq), 2.63 (dd, 1H, $J = 12.8$, 2.1 Hz, H-6eq), 2.81–2.86 (m, 1H, H-8ax), 3.10–3.19 (m, 1H, H-9ax), 3.37 (q, 1H, $J = 6.8$ Hz, CH), 6.19 (s, 1H, H-4), 6.83–8.20 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4 (CH_3), 38.3 (C-9), 48.9 (C-4), 49.8 (C-8), 55.3 (C-6), 62.3 (CH), 91.6 (C-5), 122.9, 125.4, 125.9, 126.9, 127.0, 127.1, 127.3, 127.8, 128.0, 128.3, 128.5, 128.6, 129.1, 129.2, 130.0, 131.7, 134.0, 142.4 (aromatic), 159.3 (C-3), 204.7 (C-10).

4.3.22. (4*R*,5*S*)-3-(4-Chlorophenyl)-4-(1-naphthyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 3j. Obtained as colorless crystals; mp = 146–147 °C; $[\alpha]_D = -173.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1770, 1474, 1450, 1379, 1136, 1059 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 3H, $J = 6.8$ Hz, CH_3), 1.93 (d, 1H, $J = 12.8$ Hz, H-6ax), 2.15–2.23 (m, 1H, H-8eq), 2.45–2.52 (m, 1H, H-9eq), 2.79 (dd, 1H, $J = 12.8$, 2.4 Hz, H-6eq), 2.98–3.03 (m, 1H, H-8ax), 3.16–3.23 (m, 1H, H-9ax), 3.27 (q, 1H, $J = 6.8$ Hz, CH), 6.23 (s, 1H, H-4), 6.94–8.11 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 (CH_3), 38.6 (C-9), 48.2 (C-4), 49.7 (C-8), 56.1 (C-6), 62.7 (CH), 91.2 (C-5), 122.7, 125.4, 125.7, 126.1, 126.8, 126.9, 127.2, 127.3, 127.8, 128.0, 128.3, 128.6, 128.8, 129.1, 131.7, 134.0, 135.9, 141.8 (aromatic), 158.5 (C-3), 204.2 (C-10). Anal. Calcd for $C_{31}H_{27}ClN_2O_2$: C, 75.22; H, 5.50; N, 5.66. Found: C, 75.19; H, 5.54; N, 5.62.

4.3.23. (4*S*,5*R*)-3-(4-Chlorophenyl)-4-(1-naphthyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one 4j.[16] Obtained as a colorless viscous liquid; IR ($CHCl_3$): 1728, 1574, 1442, 1359, 1150, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, 3H, $J = 6.6$ Hz, CH_3), 2.21 (d, 1H, $J = 12.9$ Hz, H-6ax), 2.37–2.44 (m, 1H, H-8eq), 2.53–2.59 (m, 1H, H-9eq), 2.63 (d, 1H, $J = 12.9$ Hz, H-6eq), 2.79–2.87 (m, 1H, H-8ax), 3.10–3.20 (m, 1H, H-9ax), 3.37 (q, 1H, $J = 6.6$ Hz, CH), 6.15 (s, 1H, H-4), 6.83–8.16 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4 (CH_3), 38.3 (C-9), 48.8 (C-4), 49.7 (C-8), 55.3 (C-6), 62.4 (CH), 91.8 (C-5), 122.8, 125.4, 126.0, 126.8, 126.9, 127.1, 127.3, 127.7, 127.9, 128.0, 128.1, 128.8, 128.9, 129.2, 131.7, 134.0, 135.9, 142.3 (aromatic), 158.4 (C-3), 204.5 (C-10).

4.4. X-ray crystallographic determination of compounds 3b and 5h

Spiroisoxazoline **3b** and spirodioxazole **5h** were recrystallized from petroleum ether–ethyl acetate (1:1) mixture. X-ray diffraction data for **3b** and **5h** were collected using a Bruker Kappa X8 APPEX II diffractometer with graphite-monochromated Mo Kα radiation $\lambda = 0.71073$ Å. The temperature of the crystal was maintained at the selected value (100 K) by means of a 700 series Cryostream cooling device to within an accuracy of ± 1. The data collection, integration, and data reduction for **3b** and **5h** were performed using Bruker SMART and Bruker SAINT programs. An empirical absorption correction was applied using psi scan method. The unit cell parameters were determined by a least square fitting of randomly selected strong reflections by SADABS program. The structure was solved by direct methods (SHELXS 97) and subsequent Fourier synthesis and refined by full matrix least squares on SHELXL 97 for all nonhydrogen atoms for **3b** and **5h**. All hydrogen atoms were placed in calculated positions.

4.4.1. Compound 3b. $C_{27}H_{25}ClN_2O_2$, $M = 444.94$, $D_c = 1.212$ g/cm^3, triclinic, space group $P1$, $a = 6.2709(4)$ Å, $b = 7.7719(5)$ Å, $c = 11.5241(7)$ Å, $V = 542.16(6)$ Å^3, $Z = 1$, $F(000) = 234$, $\mu = 0.204$ mm^{-1}. The reflections collected were 17,939 of which 6531 unique [R(int) = 0.0493]; 6531 reflections $I > 2\sigma(I)$, $R1 = 0.0251$ and $wR2 = 0.0673$ for 6531 [$I > 2\sigma(I)$] and $R1 = 0.0247$ and $wR2 = 0.0669$ for all (6607) intensity data. Goodness of fit = 1.080, residual electron density in the final Fourier map was 0.316 and -0.262 e Å^{-3}. CCDC number is 623332.

4.4.2. Compound 5h. $C_{34}H_{28}Cl_3N_3O_3$, $M = 632.94$, $D_c = 1.212$ g/cm^3, orthorhombic, space group $P2_12_12_1$, $a = 7.1329(4)$ Å, $b = 18.5932(11)$ Å, $c = 22.9836(14)$ Å, $V = 3048.2(3)$ Å^3, $Z = 4$, $F(000) = 1312$, $\mu = 0.341$ mm^{-1}. The reflections collected were 57,890 of which 14097 unique [$R(int) = 0.0249$]; 14,097 reflections $I > 2\sigma$, $R1 = 0.0496$ and $wR2 = 0.0937$ for 14,097 [$I > 2\sigma$] and $R1 = 0.0370$ and $wR2 = 0.0881$ for all (16,620) intensity data. Goodness of fit = 1.034, residual electron density in the final Fourier map was 0.477 and -0.334 e Å^{-3}. CCDC number is 623333.

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16. For **4a**–**j**, elemental analysis data and specific rotations are not given, as pure **4** could not be isolated from **3**; **4** is always obtained along with some small amounts of **3**.