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1,3-Dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones: Synthesis and antimycobacterial evaluation of enantiomerically pure spiroisoxazolidines

Raju Suresh Kumar [a], Subbu Perumal [a,*], Krithika Arun Shetty [b], Perumal Yogeeswari [b], Dharmarajan Sriram [b]

[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Palkalai Nagar, Madurai 625021, India
[b] Medicinal Chemistry & Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science, Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, Andhra Pradesh, India

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ABSTRACT

A series of novel enantiomerically pure spiroisoxazolidines were synthesized regioselectively by the 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones. These compounds have been screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Among the twenty two compounds screened, (*3S,4S,5R*)-3,4-di(4-methylphenyl)-2-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one (3e) was found to possess the maximum activity with MIC of 3.02 μM, being 2.5 times more potent than the first-line anti-TB drug ethambutol. For comparison, a series of ten enantiomerically pure spirooxazolines were also screened, among which (*4R,5S*)-3,4-bis(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one and (*4R,5S*)-4-(2-chlorophenyl)-3-(4-chlorophenyl)-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one were found to display maximum activity with MIC of 3.25 μM.

1. Introduction

The 1,3-dipolar cycloaddition is a versatile reaction for the construction of five membered ring heterocycles of biological importance [1]. Among the 1,3-dipoles, nitrones have been subjected to numerous 1,3-dipolar cycloadditions, ascribable to their stability and ease of generation [2,3]. The 1,3-dipolar cycloaddition of nitrones to alkenes afford isoxazolidines [4,5] with generation of as many as three new contiguous stereocenters in a single step [6,7]. These isoxazolidines can be further elaborated into polyfunctional cyclic or acyclic bioactive compounds with complete control of relative stereochemistry [8].

Spiro compounds display pronounced biological activities [9] and are also used in natural products chemistry for further transformation into more complex heterocycles [10]. They can be obtained from the cycloaddition of 1,3-dipoles to dipolarophiles endowed with exocyclic double bonds [11].

Piperidones and their derivatives exhibit anticancer [12], anticonvulsant [13], anti-inflammatory [14], and local anaesthetic [15] activities. Recently, we have initiated a research program on the synthesis of a series of novel heterocycles employing tandem/domino reactions [16] and/or screened them for antimycobacterial activities [17,18]. In particular, our recent investigations have disclosed that hybrid spiroheterocycles incorporating piperidone ring system in conjunction with other five membered ring systems such as pyrrolidines, pyrrolothiazoles and pyrrolizines displayed moderate to good antimycobacterial activities [19]. This prompted the synthesis of enantiomerically pure spiroisoxazolidines, comprising piperidone and isoxazolidine rings, by the 1,3-dipolar cycloaddition of (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**) with *C*-aryl-*N*-phenylnitrones and screen them for antimycobacterial activities. It is pertinent to note that in our earlier study [20], the synthesis of a series of enantiomerically pure spiroisoxazolines have been described via cycloaddition of nitrile oxides to **1** (Scheme 2). These spiroisoxazolines [20]

* Corresponding author. Tel./fax: +91 452 2459845.
E-mail address: subbu.perum@gmail.com (S. Perumal).

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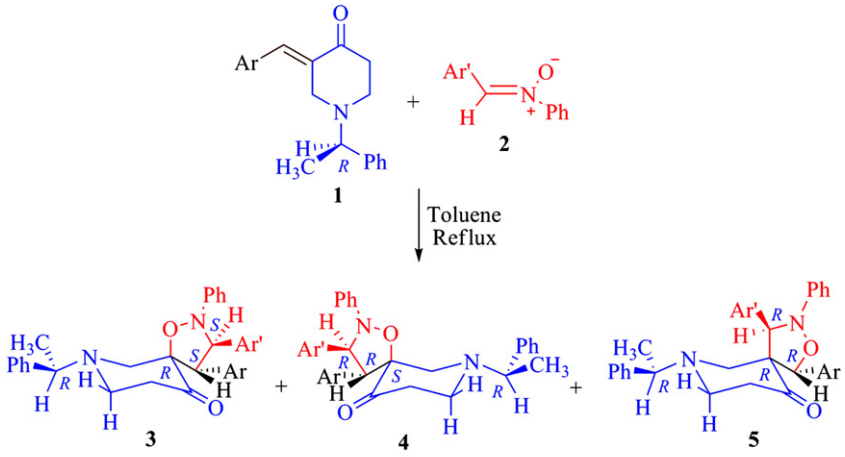
have also been screened in the present work for *in vitro* antimycobacterial activity to enable a comparison of the activity of spiroisoxazolidines and spiroisoxazolines and all these results are presented in this paper.

Tuberculosis is an infectious disease finding place amongst the worldwide health threats. The statistics released by World Health Organization reports that (i) one-third of the world's population is currently infected with TB, (ii) in each year 8 million people in worldwide develop active TB among whom about 1.7 million people die [21]. Two developments make the resurgence in TB especially alarming: (i) the pathogenic synergy with HIV resulting in an enhancement of the overall incidence of TB in HIV-positive patients [22] and (ii) the emergence of multi-drugresistant TB (MDR-TB) that resists two or more of the first-line anti-TB drugs, *viz.* isoniazid, rifampicin, pyrizinamide, ethambutol, and streptomycin [23–25]. It is also pertinent to note that in the last five decades, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB [26]. This reflects the inherent difficulties associated with the discovery and clinical testing of new candidates and the lack of significant pharmaceutical industry research in this area. Hence the discovery and development of new drugs that effectively combat TB are accorded a great importance.

2. Chemistry

In the present investigation, the 1,3-dipolar cycloaddition of (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**) with nitrones (**2**) results in the formation of spiroisoxazolidines **3–5** in moderate yields (Schemes 1). The enantiomerically pure dipolarophiles (**1**) were synthesized as described by us earlier [19]. The data presented in Scheme 1 show that the cycloaddition of (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**) with nitrones **2** proceeds regioselectively affording predominantly two diastereomeric spiroisoxazolidines, **3** and **4**, of the same regiochemistry arising from the addition of the oxygen of the nitrone to the α-carbon of the benzylidene moiety. In two cases (entries 1 and 2), spiroisoxazolidines **5a** and **5b** with reversal of the above regiochemistry, with oxygen added to the β-carbon of the benzylidene, were also obtained in addition to **3** and **4**. These results show that this cycloaddition is very sensitive to the nature of substituents in the dipolarophile and it is unclear why in two cases **5** is obtained. It is pertinent to note that in the case of entries 10 and 11, the spiroisoxazolidines, **3j** and **3k**, were obtained as the only product, while **4j** and **4k** were formed only in traces and hence their isolation proved difficult. The data presented in Scheme 1 show that the reaction is stereoselective as **3** predominates slightly over **4**. As **3** and **4** are diastereomers, they are readily separable affording enantiomerically pure spiroisoxazolidines.

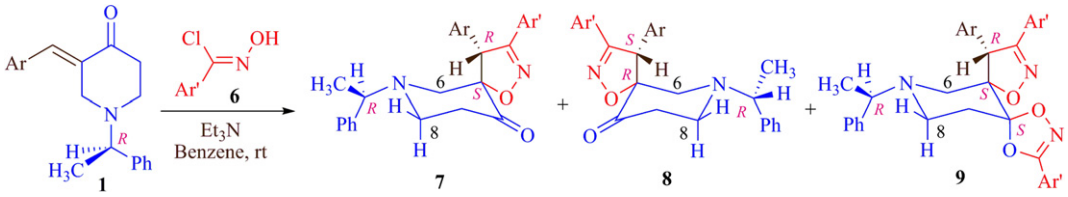
The spiroisoxazolidines were separated by flash column chromatography and their structures are in accord with their ^{1}H, ^{13}C and 2D NMR spectroscopic data as described for **4a**. The ^{1}H NMR spectrum of **4a** has two doublets at 4.45 and 4.53 ppm ($J = 7.2$ Hz) related by an H,H-COSY correlation assignable to H-3 and H-4 respectively, the *J* values indicating that H-3 and H-4 are *trans* to



Comp	Ar	Ar'	Yield[a] (%)			Time
			3	4	5	(h)
a	C_6H_5	C_6H_5	28	22	8	10
b	C_6H_5	*p*-MeC_6H_4	30	22	7	10
c	*p*-ClC_6H_4	*p*-MeC_6H_4	33	28	-	10
d	*p*-MeC_6H_4	C_6H_5	37	23	-	10
e	*p*-MeC_6H_4	*p*-MeC_6H_4	35	27	-	10
f	*o*-ClC_6H_4	C_6H_5	31	25	-	14
g	*o*-ClC_6H_4	*p*-MeC_6H_4	35	23	-	14
h	2-thienyl	C_6H_5	30	22	-	16
i	2-thienyl	*p*-MeC_6H_4	30	20	-	16
j	1-naphthyl	C_6H_5	45	[b]	-	14
k	1-naphthyl	*p*-MeC_6H_4	43	[b]	-	14

[a] Isolated yield; [b] Formed only in traces

Scheme 1. Synthesis of spiroisoxazolidines.



Scheme 2. Synthesis of spiroisoxazolines and spirodioxazoles.

each other. These assignments are supported by the HMBC correlations of (i) H-3 with the *N*-Ph *ipso* carbon at 149.3 ppm and (ii) H-4 with the carbonyl carbon at 208.3 ppm (Fig. 1). Further, H-4 shows HMBC correlations with C-3, C-5 and C-6 respectively at 78.8, 86.9 and 57.1 ppm. The C,H-COSY correlation of C-6 assigns the doublet at 1.98 ppm ($J = 13.2$ Hz) to H-6_{ax} and the doublet of doublets at 2.89 ppm ($J = 13.2$, 2.1 Hz) to H-6_{eq}. Further, H-6 shows HMBC correlations with (i) methine carbon at 62.6 ppm, (ii) methyl carbon at 19.0 ppm and (iii) the signal at 50.3 ppm due to C-8. The C,H-COSY correlation of C-8 assigns the multiplets at 2.37–2.45 and 3.04–3.13 ppm to H-8_{eq} and H-8_{ax} respectively. From the H,H-COSY correlation of H-8, it is possible to assign the multiplets at 2.37–2.45 ppm to H-9_{eq} and 3.31–3.42 ppm to H-9_{ax}. The methine and methyl protons of *N*-phenylethyl moiety appeared as a quartet at 3.57 ppm and a doublet at 1.23 ppm ($J = 6.6$ Hz) respectively. The aromatic protons appear as a multiplet in the range, 6.98–7.56 ppm. The ^{1}H and ^{13}C chemical shifts of **3a** and **4a** differ little. In the case of **3a,** the signals for H-3 and H-4 merge and appear as a singlet at 4.55 ppm. The ^{1}H and ^{13}C chemical shifts of **4a** and **3a** are shown in Figs. 2 and 3 respectively.

The ^{1}H and ^{13}C chemical shifts of all the spiroisoxazolidines **3–5** were also similarly assigned from straightforward considerations. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of the regioisomer **5a** are shown in Fig. 4. The complete stereochemistry and the configuration at the stereocentres of **5** were determined from X-ray crystallographic study of a single crystal of **5a** [27] (Fig. 5).

As all compounds belonging to series **3** and **4** were obtained as viscous liquids, X-ray crystallographic study could not be carried out. To obtain crystals suitable for X-ray crystallographic structure determination to deduce the absolute configuration at stereocentres of **3**, spiroisoxazolidine **3a** was reduced with $NaBH_4$ (Scheme 3**).** However, the alcohol **10** was obtained as a viscous liquid. Hence the spiroisoxazolidines **3d** and **4d** were converted into the corresponding oximes (Scheme 4). While **3d** afforded the oxime **11** as a viscous liquid, **4d** furnished good crystals of **12**. The structure of **12** is in agreement with the one- and two-dimensional NMR spectroscopic data and selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **12** are shown in Fig. 6. The structure of **12** determined by X-ray crystallographic study [28] (Fig. 7) provides unambiguous stereochemical information, which, in turn, establishes indirectly the complete stereochemistry of **4**. As **3** and **4** differ very little in their chemical shifts, **3** is assigned a mirror image, *viz.* enantiomeric relationship, if the configuration of the α-phenylethyl group is ignored. Thus the stereochemistry of **3** is tentatively assigned as (*3S,4S,5R*).

The low stereoselectivity observed in the cycloaddition resulting in a slightly enhanced formation of **3** relative to **4** suggests that the energies of activation for the formation of these compounds do not differ much. The formation of these diastereomers, **3** and **4** of one regiochemistry and **5** of another is explained by postulating the reaction of nitrones with two interconvertible diastereomeric conformers of **1** (Scheme 5).

The slight preference for the diastereomer **3** can be rationalized by diminished steric hindrance for the reaction of nitrone with the conformation, **1A** than with **1B** (Scheme 5) in view of the presence of the phenyl group near the C=C double bond in **1B**. The addition of nitrone over **1B** is also likely to occur from the top side leading to the axial orientation of oxygen, which is explicable by the minimum steric hindrance on this side.

3. Biological results and discussion

The compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) by agar dilution method for the determination of MIC in triplicates. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit bacterial growth. The MICs of the synthesized compounds along with the standard first-line drugs are reported in Table 1. All the compounds of spiroisoxazolidines showed promising *in-vitro* activity with MIC of less than 50 μM. Six compounds (**3e-f, 3h-i, 4e** and **4h**) inhibited MTB with MIC of less than 10 μM. Compared to the standard anti-TB drug ethambutol (MIC: 7.64 μM), five compounds (**3e, 3h, 3i, 4e** and **4h**) were found to be more active and all the twentytwo

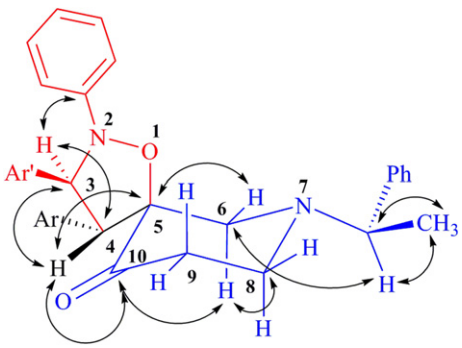


Fig. 1. Selected HMBC correlations of **4a**.

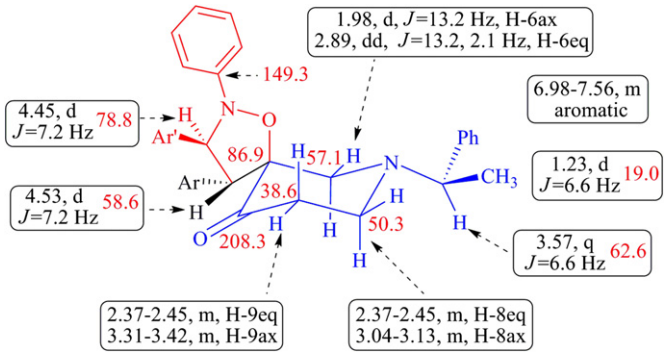


Fig. 2. ^{1}H and ^{13}C chemical shifts **4a**.

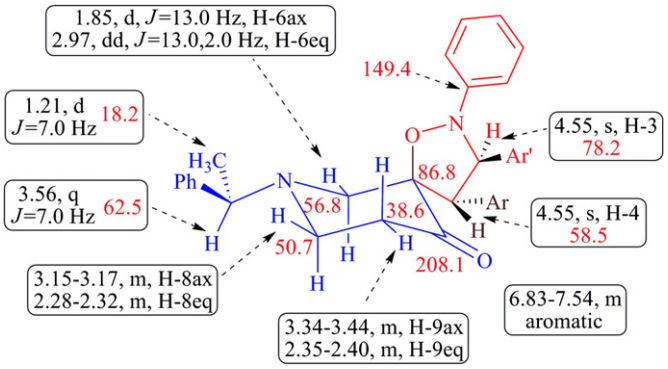


Fig. 3. ^{1}H and ^{13}C chemical shifts of **3a**.

compounds were found to be less active than isoniazid and rifampicin. (*3S*,*4S*,*5R*)-3,4-Di(4-methylphenyl)-2-phenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one (**3e**) was found to be the most active compound *in vitro* with MIC of 3.02 μM, being 2.5 times more potent than ethambutol.

An examination of the MIC values of **3** and **4** (Table 1) from structure–activity point of view reveals that four compounds belonging to one diastereomeric set, **3**, *viz.* **3e**, **3f**, **3h** and **3i** and two of the other diastereomeric set, **4**, *viz.* **4e** and **4h** are more active than the drug ethambutol. The most active candidates in series **3** and **4** are **3e** and **4e** respectively, which bear a diastereomeric relationship. It is found that all compounds belonging to **3** and **4** with substituents in the aryl rings display enhanced activity relative to the unsubstituted ones, among which **3e** and **4e** bearing a methyl group at the *para*-position of both the phenyl rings resulted in maximum activity. Replacement of the phenyl in the isoxazolidine ring (MIC of **3a** and **4a** = 25.58 μM) with the thienyl ring (MIC of **3h** and **4h** = 6.33 μM) enhances the activity four-fold, whilst substitution of the phenyl rings with bulky naphthyl ring does not alter the activity significantly.

All the compounds belonging to spiroisoxazoline **7** synthesized in our previous study [19] were also screened for *in vitro* antimycobacterial activity against MTB and the MICs along with standard drugs are given in Table 2. The data in Table 2 show that all spiroisoxazolines **7** show promising *in-vitro* activity with MIC of less than 30 μM except **7a** (MIC: 60.90 μM). Four compounds (**7d** and **7f–h**) inhibited MTB with MIC of less than 7 μM and were found to be more active than the standard anti-TB drug ethambutol (MIC: 7.64 μM). In the spiroisoxazoline series too, compounds with substituents in the aryl rings display enhanced activity than the unsubstituted ones. Compounds with Cl substitution in both the aryl rings display enhanced activity than that with unsubstituted aryl rings. Although the spiroisoxazolines **7** and the spiroisoxazolidines **3**–**5** differ in the number of aryl rings, an examination of the data in Tables 1 and 2 disclose that both these series are endowed with almost equal spread of activity.

4. Conclusion

The present investigation describes the synthesis of enantiomerically pure spiroisoxazolidines by the 1,3-dipolar cycloaddition of nitrones to enantiomerically pure dipolarophiles. The spiroheterocycles obtained in the present work display moderate to good activity against *M. tuberculosis* MTB. A series of enantiomerically pure spiroisoxazolines are found to display an almost equal antimycobacterial activity against MTB. The synthesis and screening for biological activity of further series of enantiomerically pure compounds is currently under investigation in our research group.

5. Experimental

The melting points were measured using open capillary tubes and are uncorrected. ^{1}H, ^{13}C and two-dimensional NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as 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). 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. Ten fold serial dilutions of each test compound/drug were prepared and incorporated into

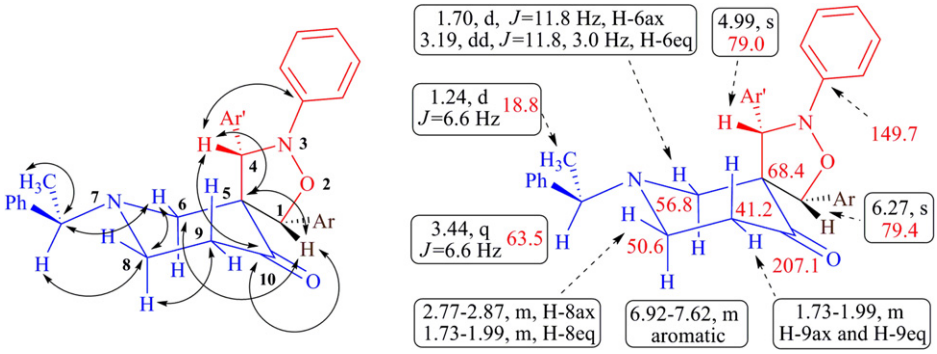


Fig. 4. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **5a**.

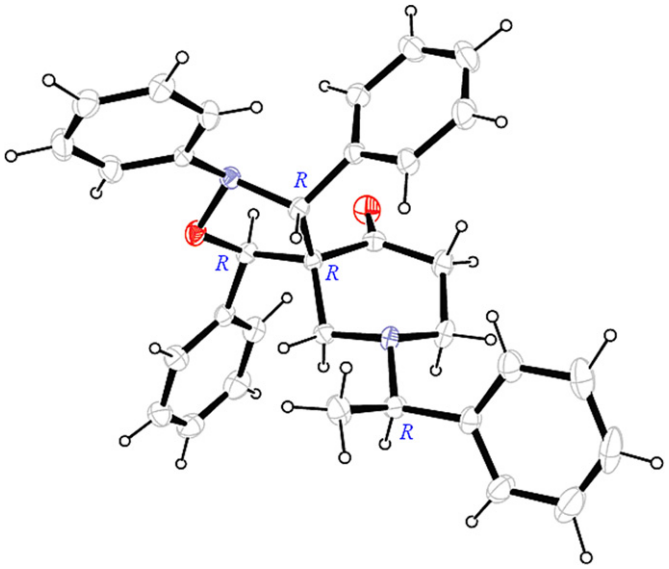


Fig. 5. ORTEP diagram of **5a**.

Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* $H_{37}Rv$ was prepared from fresh Middlebrook 7H11 agar slants with OADC Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of approximately 10^7 cfu/mL. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

5.1. Cycloaddition of C-aryl-N-phenylnitrones with 1-[(R)-1-phenylethyl]-3-[(E)-arylmethylidene]tetrahydro-4(1H)-pyridinones: general procedure

A mixture of [(*R*)-1-phenylethyl]-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone **1** (1 mmol) and nitrone **2** (1.2 mmol) in toluene (25 ml) was refluxed for 10–16 h. The progress of the reaction was monitored by TLC and after completion of the reaction, the solvent was evaporated *in vacuo* and the residue subjected to flash column chromatography on silica gel using pet ether-ethyl acetate (10:1 v/v) as eluent.

*5.1.1. (3S,4S,5R)-2,3,4-Triphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(3a)***

Colorless solid; $[\alpha]_D = +18.7$ (*c* 0.23, $CHCl_3$); Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73; Found: C, 81.16; H, 6.54; N, 5.79. IR ($CHCl_3$): 892, 1261, 1430, 1716, 2307, 2986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, 3H, $J = 7.0$ Hz, CH_3), 1.85 (d, 1H, $J = 13.0$ Hz, H-6_{ax}), 2.28–2.32 (m, 1H, H-8_{eq}), 2.35–2.40 (m, 1H, H-9_{eq}), 2.97 (dd, 1H, $J = 13.0$, 2.0 Hz, H-6_{eq}), 3.15–3.17 (m, 1H, H-8_{ax}), 3.34–3.44 (m, 1H, H-9_{ax}), 3.56 (q, 1H, $J = 7.0$ Hz, CH), 4.55 (s, 2H, H-3 and H-4), 6.83–7.54 (m, 20H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.2, 38.6, 50.7, 56.8, 58.5, 62.5, 78.2, 86.8, 117.7, 122.3, 123.2, 125.5, 127.0, 127.2, 127.4, 128.1, 128.4, 128.5, 128.7, 129.5, 137.0, 139.7, 142.7, 149.4, 208.1.

*5.1.2. (3R,4R,5S)-2,3,4-Triphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(4a)***

Viscous liquid; $[\alpha]_D = -27.0$ (*c* 0.19, $CHCl_3$); Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73; Found: C, 81.18; H, 6.65; N, 5.68. IR ($CHCl_3$): 896, 1264, 1427, 1720, 2310, 2982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.23 (d, 3H, $J = 6.6$ Hz, CH_3), 1.98 (d, 1H, $J = 13.2$ Hz, H-6_{ax}), 2.37–2.45 (m, 2H, H-8_{eq} and H-9_{eq}), 2.89 (dd, 1H, $J = 13.2$, 2.1 Hz, H-6_{eq}), 3.04–3.13 (m, 1H, H-8_{ax}), 3.31–3.42 (m, 1H, H-9_{ax}), 3.57 (q, 1H, $J = 6.6$ Hz, CH), 4.45 (d, 1H, $J = 7.2$ Hz, H-3), 4.53 (d, 1H, $J = 7.2$ Hz, H-4), 6.98–7.56 (m, 20H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.0, 38.6, 50.3, 57.1, 58.6, 62.6, 78.8, 86.9, 117.8, 123.3, 125.5, 127.0, 127.3, 127.8, 128.2, 128.4, 128.5, 128.7, 128.8, 129.5, 137.2, 139.7, 143.0, 149.3, 208.3.

*5.1.3. (1R,4R,5R)-1,3,4-Triphenyl-7-[(R)-1-phenylethyl]-2-oxa-3,7-diazaspiro[4.5]decan-10-one **(5a)***

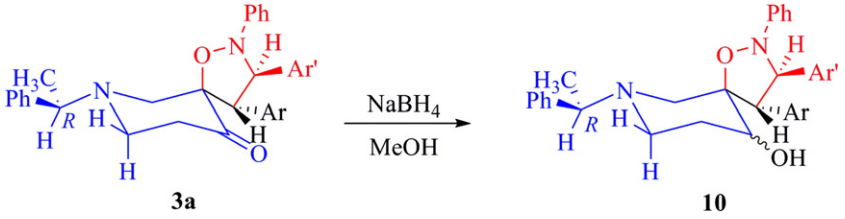
Colorless solid; $[\alpha]_D = -41.5$ (*c* 0.26, $CHCl_3$); Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73; Found: C, 81.07; H, 6.55; N, 5.69. IR (KBr): 890, 1263, 1435, 1721, 2305, 2989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.24 (d, 3H, $J = 6.6$ Hz, CH_3), 1.70 (d, 1H, $J = 11.8$ Hz, H-6_{ax}), 1.73–1.99 (m, 3H, H-8_{eq}, H-9_{ax} and H-9_{eq}), 2.77–2.87 (m, 1H, H-8_{ax}), 3.19 (dd, 1H, $J = 11.8$, 3.0 Hz, H-6_{eq}), 3.44 (q, 1H, $J = 6.6$ Hz, CH), 4.99 (s, 1H, H-4), 6.27 (s, 1H, H-1), 6.92–7.62 (m, 20H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.8, 41.2, 50.6, 56.8, 63.5, 68.4, 79.0, 79.4, 116.1, 122.4, 127.2, 127.3, 128.2, 128.3, 128.4, 128.6, 128.7, 129.4, 133.6, 134.1, 138.4, 142.9, 149.7, 207.1.

*5.1.4. (3S,4S,5R)-3-(4-Methylphenyl)-2,4-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(3b)***

Viscous liquid; $[\alpha]_D = +23.5$ (*c* 0.19, $CHCl_3$); Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.19; H, 6.88; N, 5.53. IR ($CHCl_3$): 898, 1261, 1430, 1722, 2308, 2985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, $J = 6.8$ Hz, CH_3), 1.84 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.30 (s, 1H, CH_3), 2.34–2.44 (m, 2H, H-8_{eq} and H-9_{eq}), 2.96 (dd, 1H, $J = 12.9$, 2.7 Hz, H-6_{eq}), 3.11–3.16 (m, 1H, H-8_{ax}), 3.33–3.44 (m, 1H, H-9_{ax}), 3.56 (q, 1H, $J = 6.8$ Hz, CH), 4.52 (s, 2H, H-3, H-4), 6.94–7.56 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.2,21.1, 38.9, 50.7, 56.8, 58.5, 62.5, 78.1, 86.7, 117.7, 120.9, 123.1, 127.1, 127.3, 127.4, 128.1, 128.3, 128.5, 128.8, 129.1, 129.4, 136.7, 137.3, 142.7, 149.5, 208.1.

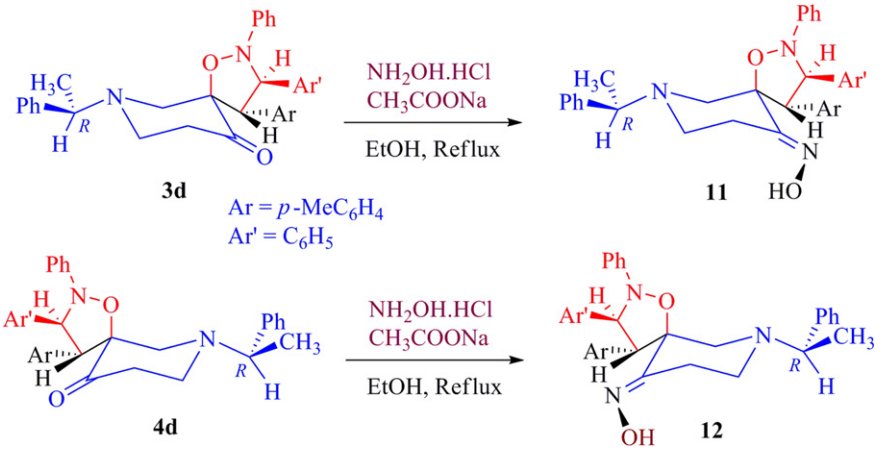
*5.1.5. (3R,4R,5S)-3-(4-Methylphenyl)-2,4-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(4b)***

Viscous liquid; $[\alpha]_D = -36.5$ (*c* 0.22, $CHCl_3$); Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.20; H, 6.75; N, 5.50. IR ($CHCl_3$): 896, 1260, 1431, 1718, 2308, 2981 cm^{-1}; ^1H NMR



3a 10

Scheme 3. Reduction of spiroisoxazolidines.



Scheme 4. Oximation of spiroisoxazolidines **3d** and **4d**.

(300 MHz, $CDCl_3$): δ_H 1.23 (d, 3H, $J = 6.8$ Hz, CH_3), 1.98 (d, 1H, $J = 13.2$ Hz, H-6_{ax}), 2.30 (s, 1H, CH_3), 2.35–2.45 (m, 2H, H-8_{eq} and H-9_{eq}), 2.88 (dd, 1H, $J = 13.2$, 1.8 Hz, H-6_{eq}), 3.06–3.10 (m, 1H, H-8_{ax}), 3.30–3.41 (m, 1H, H-9_{ax}), 3.57 (q, 1H, $J = 6.8$ Hz, CH), 4.47 (d, 1H, $J = 7.5$ Hz, H-3), 4.51 (d, 1H, $J = 7.5$ Hz, H-4), 6.98–7.28 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.0, 21.2, 38.6, 50.4, 57.2, 58.6, 62.6, 78.6, 86.8, 117.8, 123.2, 127.0, 127.1, 127.2, 127.3, 128.2, 128.3, 128.5, 129.4, 129.5, 136.6, 137.3, 137.4, 143.0, 149.4, 208.4.

5.1.6. *(1R,4R,5R)-4-(4-Methylphenyl)-1,3-diphenyl-7-[(R)-1-phenylethyl]-2-oxa-3,7-diazaspiro[4.5]decan-10-one* ***(5b)***

Viscous liquid; $[\alpha]_D = -48.8$ (*c* 0.23, $CHCl_3$); Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.29; H, 6.89; N, 5.51. IR ($CHCl_3$): 892, 1260, 1438, 1719, 2301, 2985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, $J = 6.6$ Hz, CH_3), 1.74–1.99 (m, 4H, H-6_{ax}, H-8_{eq}, H-9_{ax} and H-9_{eq}), 2.34 (s, 1H, CH_3), 2.82–2.96 (m, 2H, H-8_{ax} and H-6_{eq}), 3.42 (q, 1H, $J = 6.6$ Hz, CH), 4.87 (s, 1H, H-4), 6.13 (s, 1H, H-1), 6.84–7.44 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.8, 21.2, 41.3, 48.8, 57.6, 63.4, 68.3, 78.5, 79.9, 116.1, 122.1, 127.1, 127.3, 127.7, 128.0, 128.2, 128.5, 128.7, 128.8, 129.3, 133.6, 135.5, 138.0, 143.9, 150.1, 207.1.

5.1.7. *(3S,4S,5R)-4-(4-Chlorophenyl)-3-(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one* ***(3c)***

Viscous liquid; $[\alpha]_D = +17.5$ (*c* 0.18, $CHCl_3$); Anal. Calcd for $C_{34}H_{33}ClN_2O_2$: C, 76.03; H, 6.19; N, 5.22; Found: C, 76.09; H, 6.25; N, 5.17. IR ($CHCl_3$): 890, 1265, 1434, 1720, 2309, 2980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.25 (d, 3H, $J = 6.6$ Hz, CH_3), 1.83 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.30 (s, 1H, CH_3), 2.35–2.44 (m, 2H, H-8_{eq} and H-9_{eq}), 2.94 (dd, 1H, $J = 12.9$, 1.8 Hz, H-6_{eq}), 3.09–3.21 (m, 1H, H-8_{ax}), 3.39 (td, 1H, $J = 12.0$, 6.0 Hz, H-9_{ax}), 3.60 (q, 1H, $J = 6.6$ Hz, CH), 4.42 (d, 1H, $J = 7.5$ Hz, H-3), 4.51 (d, 1H, $J = 7.5$ Hz, H-4), 6.99–7.29 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.1, 21.2, 38.8, 50.7, 56.7, 57.9, 62.4, 78.3, 86.5, 117.7, 123.3, 127.0, 127.4, 128.2, 128.5, 128.8, 129.1, 129.4, 130.8, 133.2, 135.7, 136.2, 137.6, 142.7, 149.3, 207.9.

5.1.8. *(3R,4R,5S)-4-(4-Chlorophenyl)-3-(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one* ***(4c)***

Viscous liquid; $[\alpha]_D = -44.0$ (*c* 0.23, $CHCl_3$); Anal. Calcd for $C_{34}H_{33}ClN_2O_2$: C, 76.03; H, 6.19; N, 5.22; Found: C, 76.10; H, 6.14; N, 5.28. IR ($CHCl_3$): 892, 1261, 1430, 1718, 2309, 2986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.27 (d, 3H, $J = 6.6$ Hz, CH_3), 1.90 (d, 1H, $J = 13.0$ Hz, H-6_{ax}), 2.31 (s, 1H, CH_3), 2.35–2.46 (m, 2H, H-8_{eq} and H-9_{eq}), 2.85 (d, 1H, $J = 13.0$ Hz, H-6_{eq}), 3.05–3.21 (m, 1H, H-8_{ax}), 3.33–3.44 (m, 1H, H-9_{ax}), 3.56 (q, 1H, $J = 6.6$ Hz, CH), 4.37 (d, 1H, $J = 7.2$ Hz, H-3), 4.50 (d, 1H, $J = 7.2$ Hz, H-4), 7.01–7.30 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.0, 21.2, 38.6, 50.3, 57.4, 57.8, 62.7, 78.7, 86.6, 117.9, 123.4, 127.1, 127.2, 127.3, 128.2, 128.5, 128.8, 129.1, 129.4, 133.1, 135.9, 136.2, 137.6, 143.0, 149.2, 208.1.

5.1.9. *(3S,4S,5R)-4-(4-Methylphenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one* ***(3d)***

Viscous liquid; $[\alpha]_D = +20.7$ (*c* 0.24, $CHCl_3$); Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.19; H, 6.86; N,

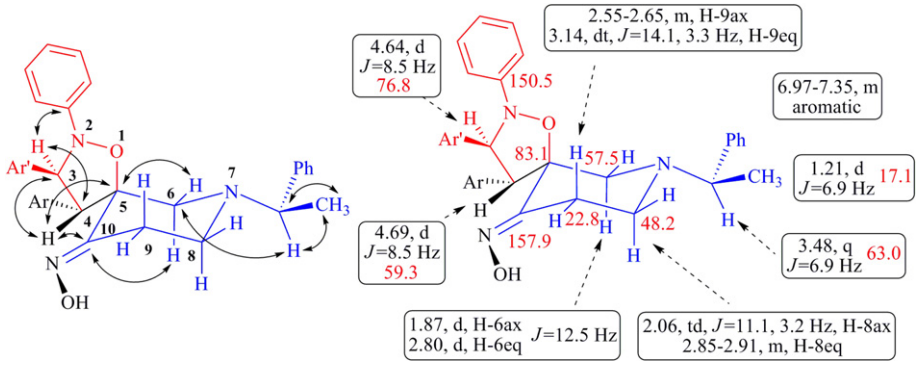


Fig. 6. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **12**.

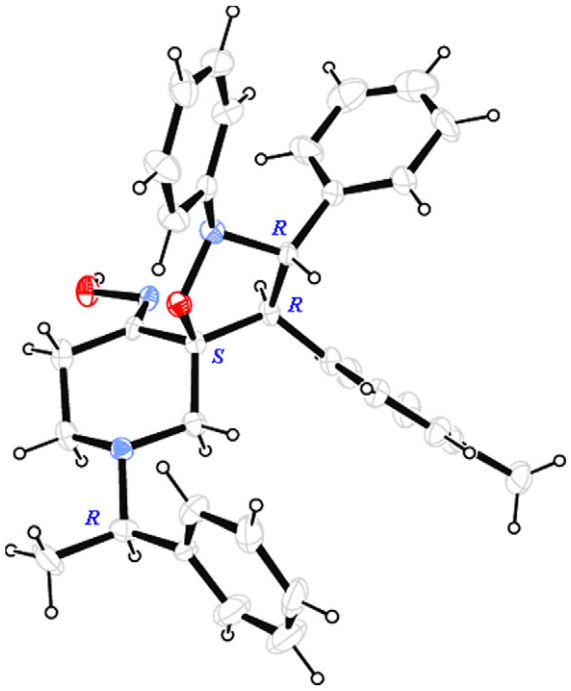


Fig. 7. ORTEP diagram for **12**.

5.63. IR ($CHCl_3$): 894, 1262, 1430, 1718, 2309, 2983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, 3H, $J = 6.8$ Hz, CH_3), 1.87 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.25–2.44 (m, 5H, CH_3, H-8_{eq} and H-9_{eq}), 3.00 (dd, 1H, $J = 12.9$, 2.4 Hz, H-6_{eq}), 3.07–3.16 (m, 1H, H-8_{ax}), 3.31–3.41 (m, 1H, H-9_{ax}), 3.54 (q, 1H, $J = 6.8$ Hz, CH), 4.50 (d, 1H, $J = 7.8$ Hz, H-4), 4.54 (d, 1H, $J = 7.8$ Hz, H-3), 6.98–7.30 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.4, 21.0, 39.0, 50.7, 56.9, 58.3, 62.6, 78.1, 86.7, 117.6, 123.1, 127.0, 127.2, 127.4, 127.7, 128.1, 128.5, 128.6, 129.1, 129.4, 133.7, 136.9, 139.8, 143.0, 149.6, 208.1.

5.1.10. (3R,4R,5S)-4-(4-Methylphenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(4d)***

Viscous liquid; $[\alpha]_D = -25.8$ (c 0.21, $CHCl_3$); Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57; Found: C, 81.20; H, 6.77; N, 5.54. IR ($CHCl_3$): 894, 1266, 1436, 1721, 2307, 2989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.24 (d, 3H, $J = 6.9$ Hz, CH_3), 2.01 (d, 1H, $J = 13.1$ Hz, H-6_{ax}), 2.31 (s, 1H, CH_3), 2.35–2.45 (m, 2H, H-8_{eq} and H-9_{eq}), 2.89 (dd, 1H, $J = 13.1$, 2.4 Hz, H-6_{eq}), 3.01–3.12 (m, 1H, H-8_{ax}), 3.31–3.41 (m, 1H, H-9_{ax}), 3.59 (q, 1H, $J = 6.9$ Hz, CH), 4.46–4.51 (m, 2H, H-3, H-4), 7.05–7.54 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.8, 21.0, 38.6, 50.2, 57.2, 58.2, 62.5, 78.6, 86.9, 117.7, 122.3, 126.9, 127.2, 127.3, 127.7, 128.1, 128.5, 128.6, 129.0, 129.3, 134.0, 136.9, 139.7, 143.2, 149.4, 208.3.

5.1.11. (3S,4S,5R)-3,4-Di(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(3e)***

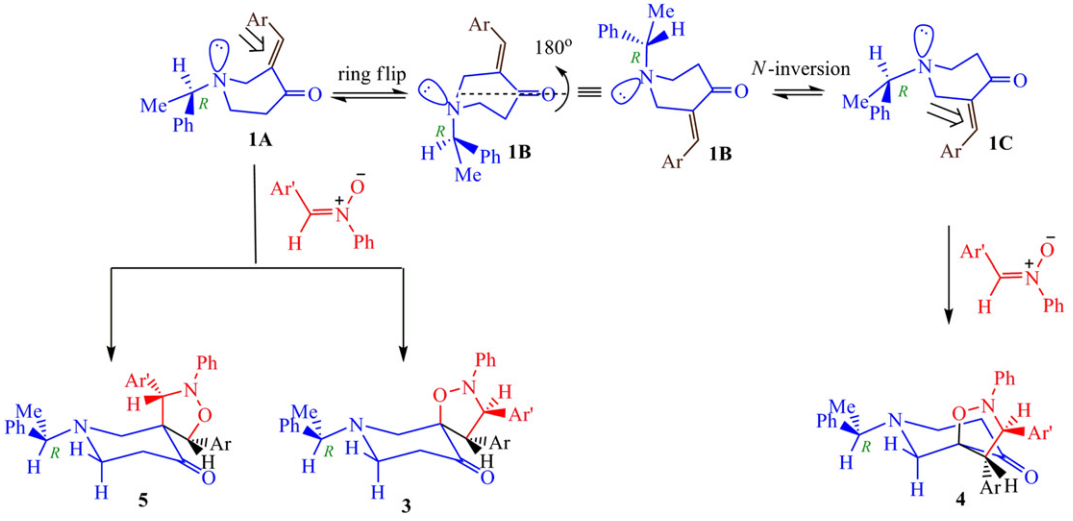
Viscous liquid; $[\alpha]_D = +13.5$ (c 0.22, $CHCl_3$); Anal. Calcd for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.02; N, 5.42; Found: C, 81.30; H, 7.07; N, 5.37. IR ($CHCl_3$): 892, 1261, 1430, 1716, 2304, 2985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, 3H, $J = 6.6$ Hz, CH_3), 1.87 (d, 1H, $J = 12.8$ Hz, H-6_{ax}), 2.30 (s, 1H, CH_3), 2.31 (s, 1H, CH_3), 2.33–2.42 (m, 2H, H-8_{eq} and H-9_{eq}), 2.99 (dd, 1H, $J = 12.8$, 2.1 Hz, H-6_{eq}), 3.06–3.15 (m, 1H, H-8_{ax}), 3.30–3.41 (m, 1H, H-9_{ax}), 3.54 (q, 1H, $J = 6.6$ Hz, CH), 4.46–4.52 (m, 2H, H-3, H-4), 6.97–7.30 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.3, 21.0, 21.2, 39.0, 50.7, 56.9, 58.3, 62.5, 77.9, 86.6, 117.6, 123.0, 126.9, 127.1, 127.4, 128.1, 128.5, 128.6, 129.0, 129.3, 129.4, 133.8, 136.7, 137.3, 143.0, 149.6, 208.1.

5.1.12. (3R,4R,5S)-3,4-Di(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(4e)***

Viscous liquid; $[\alpha]_D = -34.0$ (c 0.18, $CHCl_3$); Anal. Calcd for $C_{35}H_{36}N_2O_2$: C, 81.36; H, 7.02; N, 5.42%; Found: C, 81.40; H, 7.08; N, 5.47. IR ($CHCl_3$): 896, 1265, 1427, 1720, 2310, 2981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.24 (d, 3H, $J = 6.8$ Hz, CH_3), 2.01 (d, 1H, $J = 13.1$ Hz, H-6_{ax}), 2.30 (s, 1H, CH_3), 2.31 (s, 1H, CH_3), 2.33–2.45 (m, 2H, H-8_{eq} and H-9_{eq}), 2.88 (dd, 1H, $J = 13.1$, 2.4 Hz, H-6_{eq}), 3.01–3.12 (m, 1H, H-8_{ax}), 3.30–3.40 (m, 1H, H-9_{ax}), 3.59 (q, 1H, $J = 6.8$ Hz, CH), 4.43–4.48 (m, 2H, H-3, H-4), 6.98–7.27 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.9, 21.1, 21.2, 38.6, 50.2, 57.2, 58.2, 62.5, 78.4, 86.9, 117.7, 123.1, 127.0, 127.2, 127.3, 128.2, 128.5, 129.0, 129.3, 129.4, 134.1, 136.7, 136.8, 137.3, 143.2, 149.5, 208.4.

5.1.13. (3S,4S,5R)-4-(2-Chlorophenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(3f)***

Viscous liquid; $[\alpha]_D = +18.5$ (c 0.21, $CHCl_3$); Anal. Calcd for $C_{33}H_{31}ClN_2O_2$: C, 75.78; H, 5.97; N, 5.36; Found: C, 75.72; H, 5.93; N, 5.42. IR ($CHCl_3$): 895, 1267, 1432, 1716, 2304, 2982 cm^{-1}; ^1H NMR



Scheme 5. Formation of spiroisoxazolidines.

Table 1
Anti-tubercular activity of spiroisoxazolidines **3–5** against MTB.

Comp	MIC (μM)		
	3	4	5
a	25.58	25.58	25.58
b	49.74	49.74	24.89
c	23.27	11.64	–
d	24.89	12.43	–
e	3.02	6.06	–
f	5.98	23.90	–
g	11.64	11.64	–
h	6.33	6.33	–
i	6.15	24.57	–
j	23.20	–	–
k	22.62	–	–
Isoniazid			0.36
Rifampicin			0.12
Ciprofloxacin			4.71
Ethambutol			7.64

(300 MHz, $CDCl_3$): δ_H 1.17 (d, 3H, $J = 6.6$ Hz, CH_3), 2.03 (d, 1H, $J = 12.6$ Hz, H-6_{ax}), 2.35–2.56 (m, 2H, H-8_{eq} and H-9_{eq}), 2.78 (d, 1H, $J = 12.6$ Hz, H-6_{eq}), 3.02–3.13 (m, 1H, H-8_{ax}), 3.23–3.38 (m, 1H, H-9_{ax}), 3.59 (q, 1H, $J = 6.6$ Hz, CH), 4.52 (d, 1H, $J = 6.6$ Hz, H-3), 5.27 (d, 1H, $J = 6.6$ Hz, H-4), 7.00–7.56 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.8, 38.6, 50.7, 54.0, 55.8, 62.3, 78.6, 86.6, 117.7, 122.3, 123.3, 125.5, 126.7, 127.0, 127.2, 127.4, 128.1, 128.5, 128.7, 128.8, 129.6, 131.6, 135.7, 139.5, 142.7, 149.0, 207.2.

*5.1.14. (3R,4R,5S)-4-(2-Chlorophenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(4f)***

Viscous liquid; $[\alpha]_D = -22.0$ (*c* 0.17, $CHCl_3$); Anal. Calcd for $C_{33}H_{31}ClN_2O_2$: C, 75.78; H, 5.97; N, 5.36; Found: C, 75.74; H, 6.03; N, 5.30. IR ($CHCl_3$): 890, 1264, 1432, 1718, 2308, 2985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.16 (d, 3H, $J = 6.3$ Hz, CH_3), 2.23 (d, 1H, $J = 12.6$ Hz, H-6_{ax}), 2.47–2.60 (m, 2H, H-8_{eq} and H-9_{eq}), 2.69 (d, 1H, $J = 12.6$ Hz, H-6_{eq}), 2.88–3.00 (m, 1H, H-8_{ax}), 3.14–3.27 (m, 1H, H-9_{ax}), 3.45 (q, 1H, $J = 6.3$ Hz, CH), 4.51 (d, 1H, $J = 6.0$ Hz, H-3), 5.21 (d, 1H, $J = 6.0$ Hz, H-4), 6.99–7.53 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.5, 38.4, 50.3, 54.5, 56.6, 62.8, 78.9, 86.8, 117.5, 120.1, 123.2, 126.7, 127.0, 127.2, 127.8, 128.2, 128.4, 128.5, 128.7, 129.1, 129.7, 135.2, 135.9, 139.6, 143.2, 149.1, 207.3.

*5.1.15. (3S,4S,5R)-4-(2-Chlorophenyl)-3-(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(3g)***

Viscous liquid; $[\alpha]_D = +16.5$ (*c* 0.17, $CHCl_3$); Anal. Calcd for $C_{34}H_{33}ClN_2O_2$: C, 76.03; H, 6.19; N, 5.22; Found: C, 76.08; H, 6.25; N, 5.28. IR ($CHCl_3$): 892, 1264, 1430, 1718, 2309, 2986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 1.16 (d, 3H, $J = 6.6$ Hz, CH_3), 2.03 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.31 (s, 1H, CH_3), 2.37–2.48 (m, 2H, H-8_{eq} and H-9_{eq}), 2.77 (d, 1H, $J = 12.9$ Hz, H-6_{eq}), 3.02–3.12 (m, 1H, H-8_{ax}), 3.23–3.37 (m, 1H, H-9_{ax}), 3.58 (q, 1H, $J = 6.6$ Hz, CH), 4.49 (d, 1H, $J = 6.3$ Hz, H-3), 5.24 (d, 1H, $J = 6.3$ Hz, H-4), 7.09–7.39 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 17.8, 21.2, 38.6, 50.7, 54.0, 55.8, 62.3, 78.4, 86.5, 117.7, 120.9, 123.2, 126.6, 127.0, 127.1, 127.4, 128.1, 128.3, 128.5, 128.8, 129.4, 129.7, 135.8, 136.4, 137.4, 142.7, 149.0, 207.3.

Table 2
Anti-tubercular activity of spiroisoxazolines **7** against MTB.

Comp 7	Ar	Ar′	MIC (μM)
a	C_6H_5	C_6H_5	60.90
b	C_6H_5	*p*-ClC_6H_4	14.05
c	*p*-ClC_6H_4	C_6H_5	14.05
d	*p*-ClC_6H_4	*p*-ClC_6H_4	3.25
e	*p*-$CH_3C_6H_4$	C_6H_5	14.72
f	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	6.82
g	*o*-ClC_6H_4	C_6H_5	7.03
h	*o*-ClC_6H_4	*p*-ClC_6H_4	3.25
i	1-naphthyl	C_6H_5	27.14
j	1-naphthyl	*p*-ClC_6H_4	25.25
Isoniazid			0.36
Rifampicin			0.12
Ciprofloxacin			4.71
Ethambutol			7.64

*5.1.16. (3R,4R,5S)-4-(2-Chlorophenyl)-3-(4-methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(4g)***

Viscous liquid; $[\alpha]_D = -41.0$ (*c* 0.26, $CHCl_3$); Anal. Calcd for $C_{34}H_{33}ClN_2O_2$: C, 76.03; H, 6.19; N, 5.22; Found: C, 76.10; H, 6.14; N, 5.26. IR ($CHCl_3$): 891, 1261, 1432, 1720, 2311, 2982 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 1.15 (d, 3H, $J = 6.3$ Hz, CH_3), 2.23 (d, 1H, $J = 12.6$ Hz, H-6_{ax}), 2.48–2.58 (m, 2H, H-8_{eq} and H-9_{eq}), 2.67 (d, 1H, $J = 12.6$ Hz, H-6_{eq}), 2.87–3.00 (m, 1H, H-8_{ax}), 3.13–3.27 (m, 1H, H-9_{ax}), 3.44 (q, 1H, $J = 6.3$ Hz, CH), 4.48 (d, 1H, $J = 6.2$ Hz, H-3), 5.18 (d, 1H, $J = 6.2$ Hz, H-4), 6.99–7.54 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 19.4, 21.2, 38.4, 50.3, 54.5, 56.5, 62.8, 78.7, 86.7, 117.5, 120.8, 122.3, 123.1, 128.5, 127.0, 127.2, 128.2, 128.5, 128.7, 128.8, 129.4, 129.6, 131.6, 136.5, 137.4, 143.9, 149.1, 207.3.

*5.1.17. (3S,4S,5R)-2,3-Diphenyl-7-[(R)-1-phenylethyl]-4-(2-thienyl)-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(3h)***

Viscous liquid; $[\alpha]_D = +19.0$ (*c* 0.21, $CHCl_3$); Anal. Calcd for $C_{31}H_{30}N_2O_2S$: C, 75.27; H, 6.11; N, 5.66; Found: C, 75.22; H, 6.15; N, 5.60. IR ($CHCl_3$): 890, 1268, 1430, 1715, 2309, 2986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 1.26 (d, 3H, $J = 6.8$ Hz, CH_3), 2.01 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.17–2.40 (m, 2H, H-8_{eq} and H-9_{eq}), 3.13–3.17 (m, 2H, H-6_{eq}, H-8_{ax}), 3.35 (td, 1H, $J = 12.3$, 5.7 Hz, H-9_{ax}), 3.54 (q, 1H, $J = 6.6$ Hz, CH), 4.49 (d, 1H, $J = 8.4$ Hz, H-3), 4.96 (d, 1H, $J = 8.4$ Hz, H-4), 6.85–7.57 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.7, 39.1, 50.5, 54.0, 56.7, 62.8, 78.9, 86.1, 118.0, 123.6, 124.8, 126.9, 127.0, 127.4, 127.5, 128.0, 128.2, 128.5, 128.7, 128.8, 138.8, 138.9, 142.8, 149.4, 207.0.

*5.1.18. (3R,4R,5S)-2,3-Diphenyl-7-[(R)-1-phenylethyl]-4-(2-thienyl)-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(4h)***

Viscous liquid; $[\alpha]_D = -28.0$ (*c* 0.22, $CHCl_3$); Anal. Calcd for $C_{31}H_{30}N_2O_2S$: C, 75.27; H, 6.11; N, 5.66; Found: C, 75.32; H, 6.16; N, 5.70. IR ($CHCl_3$): 895, 1264, 1436, 1720, 2309, 2985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 1.31 (d, 3H, $J = 6.6$ Hz, CH_3), 2.14 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.38–2.46 (m, 2H, H-8_{eq} and H-9_{eq}), 3.04–3.15 (m, 2H, H-6_{eq}, H-8_{ax}), 3.30–3.44 (m, 1H, H-9_{ax}), 3.69 (q, 1H, $J = 6.6$ Hz, CH), 4.41 (d, 1H, $J = 8.3$ Hz, H-3), 4.96 (d, 1H, $J = 8.3$ Hz, H-4), 6.93–7.49 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 18.6, 38.7, 50.1, 53.8, 56.6, 62.5, 79.6, 86.3, 118.4, 122.3, 123.8, 125.9, 126.9, 127.0, 127.3, 127.6, 128.5, 128.7, 128.8, 129.1, 138.6, 139.2, 142.6, 149.1, 207.5.

*5.1.19. (3S,4S,5R)-3-(4-Methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-4-(2-thienyl)-1-oxa-2,7-diazaspiro[4.5]decan-10-one **(3i)***

Viscous liquid; $[\alpha]_D = +21.0$ (*c* 0.24, $CHCl_3$); Anal. Calcd for $C_{32}H_{32}N_2O_2S$: C, 75.56; H, 6.34; N, 5.51; Found: C, 75.59; H, 6.39; N, 5.57. IR ($CHCl_3$): 894, 1268, 1438, 1719, 2307, 2986 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):δ_H 1.25 (d, 3H, $J = 6.6$ Hz, CH_3), 2.07 (d, 1H, $J = 13.2$ Hz, H-6_{ax}), 2.17–2.40 (m, 5H, CH_3, H-8_{eq}, H-9_{eq}), 3.09–3.18 (m, 2H, H-6_{eq}, H-8_{ax}), 3.34 (td, 1H, $J = 12.6$, 5.7 Hz, H-9_{ax}), 3.53 (q, 1H, $J = 6.6$ Hz, CH), 4.45 (d, 1H, $J = 8.5$ Hz, H-3), 4.93 (d, 1H, $J = 8.5$ Hz, H-4), 6.84–7.81 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.6, 21.2, 39.1, 50.5, 54.0, 56.7, 62.8, 78.7, 85.9, 118.0,

120.8, 123.5, 124.7, 125.7, 126.9, 127.0, 127.4, 128.2, 128.5, 128.8, 129.1, 129.4, 137.7, 139.0, 142.8, 149.5, 207.1.

5.1.20. (3R,4R,5S)-3-(4-Methylphenyl)-2-phenyl-7-[(R)-1-phenylethyl]-4-(2-thienyl)-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(4i)***

Viscous liquid; $[\alpha]_D = -32.0$ (*c* 0.19, $CHCl_3$); Anal. Calcd for $C_{32}H_{32}N_2O_2S$: C, 75.56; H, 6.34; N, 5.51; Found: C, 75.50; H, 6.38; N, 5.45. IR ($CHCl_3$): 890, 1268, 1431, 1722, 2305, 2983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ_H 1.31 (d, 3H, $J = 6.9$ Hz, CH_3), 2.13 (d, 1H, $J = 12.9$ Hz, H-6_{ax}), 2.30–2.37 (m, 5H, CH_3, H-8_{eq} and H-9_{eq}), 3.02–3.15 (m, 2H, H-6_{eq}, H-8_{ax}), 3.28–3.41 (m, 1H, H-9_{ax}), 3.64 (q, 1H, $J = 6.9$ Hz, CH), 4.38 (d, 1H, $J = 8.3$ Hz, H-3), 4.93 (d, 1H, $J = 8.3$ Hz, H-4), 6.82–7.81 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 18.6, 21.2, 38.7, 50.1, 53.8, 56.7, 62.5, 79.4, 86.2, 118.4, 123.7, 124.7, 127.2, 127.4, 127.5, 128.2, 128.5, 129.0, 129.4, 135.5, 136.7, 139.3, 143.2, 149.2, 207.5.

5.1.21. (3S,4S,5R)-4-(1-Naphthyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(3j)***

Viscous liquid; $[\alpha]_D = +29.0$ (*c* 0.27, $CHCl_3$); Anal. Calcd for $C_{37}H_{34}N_2O_2$: C, 82.50; H, 6.36; N, 5.20; Found: C, 82.56; H, 6.43; N, 5.14. IR ($CHCl_3$): 893, 1264, 1431, 1720, 2307, 2986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ_H 1.20 (d, 3H, $J = 6.6$ Hz, CH_3), 1.83 (d, 1H, $J = 13.2$ Hz, H-6_{ax}), 2.29–2.38 (m, 1H, H-8_{eq}), 2.43 (dt, $J = 12.6$, 3.3 Hz, 1H, H-9_{eq}), 2.84 (dd, 1H, $J = 13.2$, 2.4 Hz, H-6_{eq}), 3.02–3.10 (m, 1H, H-8_{ax}), 3.40–3.48 (m, 1H, H-9_{ax}), 3.51 (q, 1H, $J = 6.6$ Hz, CH), 4.76 (d, 1H, $J = 7.2$ Hz, H-4), 5.68 (d, 1H, $J = 7.2$ Hz, H-3), 7.10–7.84 (m, 22H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 19.1, 38.4, 50.3, 52.0, 56.6, 62.2, 79.0, 87.0, 118.2, 123.3, 123.6, 124.9, 125.7, 125.9, 126.6, 126.9, 127.2, 127.5, 127.8, 128.1, 128.3, 128.5, 128.7, 129.5, 132.9, 133.3, 133.8, 139.7, 143.2, 149.2, 208.9.

5.1.22. (3R,4R,5S)-3-(4-Methylphenyl)-4-(1-naphthyl)-2-phenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one ***(3k)***

Viscous liquid; $[\alpha]_D = +26.5$ (*c* 0.25, $CHCl_3$); Anal. Calcd for $C_{38}H_{36}N_2O_2$: C, 82.58; H, 6.57; N, 5.07; Found: C, 82.52; H, 6.52; N, 5.13. IR ($CHCl_3$): 891, 1267, 1438, 1721, 2311, 2989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):δ_H 1.16 (d, 3H, $J = 6.6$ Hz, CH_3), 1.83 (d, 1H, $J = 13.0$ Hz, H-6_{ax}), 2.25 (s, 1H, CH_3), 2.29–2.45 (m, 2H, H-8_{eq} and H-9_{eq}), 2.83 (dd, 1H, $J = 13.0$, 2.7 Hz, H-6_{eq}), 3.02–3.12 (m, 1H, H-8_{ax}), 3.40–3.44 (m, 1H, H-9_{ax}), 3.48 (q, 1H, $J = 6.6$ Hz, CH), 4.73 (d, 1H, $J = 7.4$ Hz, H-4), 5.66 (d, 1H, $J = 7.4$ Hz, H-3), 7.02–7.83 (m, 22H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$):δ_C 19.1, 21.1, 38.4, 50.3, 52.0, 56.6, 62.2, 78.8, 86.9, 118.1, 123.5, 124.9, 125.6, 125.9, 126.5, 126.9, 127.0, 127.2, 127.3, 127.8, 128.1, 128.5, 129.0, 129.3, 129.4, 133.0, 133.4, 133.8, 137.4, 143.2, 149.2, 208.9.

5.2. Oximation of 4-(4-methylphenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one. General procedure

4-(4-Methylphenyl)-2,3-diphenyl-7-[(*R*)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one **4d** (0.05 g, 0.1 mmol), hydroxylammonium chloride (0.010 g, 0.14 mmol) and sodium acetate (0.011 g, 0.14 mmol) in ethanol (3 ml) was refluxed for 30 min. After completion of the reaction as evident from TLC, the excess solvent was evaporated *in vacuo* and the residue subjected to flash column chromatography on silica gel using petroleum ether-ethyl acetate (10:2) as eluent.

5.2.1. (3S,4S,5R)-4-(4-Methylphenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one oxime ***(11)***

Viscous liquid; $[\alpha]_D = +36.8$ (*c* 0.16, $CHCl_3$); Anal. Calcd for $C_{34}H_{35}N_3O_2$: C, 78.89; H, 6.81; N, 8.12; Found: C, 78.82; H, 6.86; N, 8.18. ^1H NMR (300 MHz, $CDCl_3$):δ_H 1.16 (d, 3H, $J = 6.8$ Hz, CH_3), 1.80 (d, 1H, $J = 12.3$ Hz, H-6_{ax}), 1.86 (td, 1H, $J = 11.4$, 2.9 Hz, H-8_{ax}), 2.31 (s, 1H, CH_3), 2.45–2.56 (m, 1H, H-9_{ax}), 2.84–2.93 (m, 1H, H-8_{eq}), 2.99 (d, 1H, $J = 12.3$ Hz, H-6_{eq}), 3.14 (dt, 1H, $J = 14.1$, 3.0 Hz, H-9_{eq}), 3.35 (q, 1H, $J = 6.8$ Hz, CH), 4.71 (d, 1H, $J = 8.9$ Hz, H-4), 4.79 (d, 1H, $J = 8.9$ Hz, H-3), 6.92–7.37 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.6, 21.1, 23.1, 48.6, 57.0, 59.4, 63.6, 76.2, 83.6, 116.2, 122.0, 126.8, 127.0, 127.4, 127.5, 128.1, 128.4, 128.5, 128.9, 129.8, 133.1, 136.8, 140.7, 143.0, 151.1, 157.3.

5.2.2. (3R,4R,5S)-4-(4-Methylphenyl)-2,3-diphenyl-7-[(R)-1-phenylethyl]-1-oxa-2,7-diazaspiro[4.5]decan-10-one oxime ***(12)***

Colorless crystals; $[\alpha]_D = -32.0$ (*c* 0.19, $CHCl_3$); Anal. Calcd for $C_{34}H_{35}N_3O_2$: C, 78.89; H, 6.81; N, 8.12; Found: C, 78.95; H, 6.77; N, 8.17. ^1H NMR (300 MHz, $CDCl_3$):δ_H 1.21 (d, 3H, $J = 6.9$ Hz, CH_3), 1.87 (d, 1H, $J = 12.5$ Hz, H-6_{ax}), 2.06 (td, 1H, $J = 11.1$, 3.2 Hz, H-8_{ax}), 2.32 (s, 1H, CH_3), 2.55–2.65 (m, 1H, H-9_{ax}), 2.80 (d, 1H, $J = 12.5$ Hz, H-6_{eq}), 2.85–2.91 (m, 1H, H-8_{eq}), 3.14 (dt, 1H, $J = 14.1$, 3.3 Hz, H-9_{eq}), 3.48 (q, 1H, $J = 6.9$ Hz, CH), 4.64 (d, 1H, $J = 8.5$ Hz, H-3), 4.69 (d, 1H, $J = 8.5$ Hz, H-4), 6.97–7.35 (m, 19H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.1, 21.1, 22.8, 48.2, 57.5, 59.3, 63.0, 76.8, 83.1, 116.8, 122.3, 126.8, 127.2, 127.5, 127.6, 128.0, 128.4, 128.5, 128.8, 129.6, 133.6, 136.8, 140.4, 142.7, 150.5, 157.9.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.ejmech.2009.09.034.

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