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Axially Chiral *N*-(*o*-aryl)-4-Hydroxy-2-oxazolidinone Derivatives from Diastereoselective Reduction of *N*-(*o*-aryl)-2,4-oxazolidinediones: Thermally Interconvertible Atropisomers via Ring-Chain-Ring Tautomerization

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ABSTRACT The reduction of the axially chiral *N*-(*o*-aryl)-5,5-dimethyl-2,4-oxazolidinediones by $NaBH_4$ yielded axially chiral *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone enantiomers having a chiral center at C-4, with 100% diastereoselectivity as has been shown by their ^1H and ^{13}C NMR spectra and by enantioselective HPLC analysis. The resolved enantiomeric isomers were found to interconvert thermally through an aldehyde intermediate formed upon ring cleavage via a latent ring-chain-ring tautomerization. It was found that the rate of enantiomerization depended on the size and the electronic effect of the *ortho* substituent present on the aryl ring bonded to the nitrogen of the heterocycle. *Chirality 22:641–654, 2010.*

KEY WORDS: axial chirality; diastereoselective reduction; ring-chain-ring tautomerization; enantioselective HPLC; enantiomer separation; barrier to enantiomerization; 2,4-oxazolidinediones; temperature-dependent NMR

INTRODUCTION

The heterocyclic analogs of biphenyls of the type *N*-(*o*-aryl)-2,4-oxazolidinediones (±)**1–6** (Scheme 1) have ground states where the two rings are orthogonal to each other and are thus axially chiral.[1–3] The enantiomers of these compounds are known to racemize thermally *via* rotation around the N_{sp2}-C_{aryl} bond,[2,3] through a planar transition state (Scheme 1). In fact the activation barriers determined for these[2,3] and structurally similar systems[4] revealed that there is a linear relationship between the van der Waals radius of the *ortho* halogen substituent and the activation barrier to hindered rotation.

The reduction of unsymmetrical anhydrides[5] and cyclic amides with $NaBH_4$ are known to be regioselective.[6] The hydride attack takes place on the carbonyl group that is vicinal to the most substituted carbon. We therefore expect the regioselective reduction at C-4 carbon in compounds (±)**1–6** which will result in the synthesis of the axially chiral *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones (see Fig. 1) having a chiral center at C-4 of the ring. The synthesis of these compounds, their chromatographic resolutions and study of their barriers to enantiomerization carried out in this work are considered important because such compounds may have a potential to be used as axially chiral non-biaryl auxiliaries[7] and bidentate ligands[8] with suitable *ortho* substituents. For example, the *N*-(*o*-hydroxyphenyl) substituted *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones would be analogous to the well known BINOL.[9]

This article describes the regio and diastereoselective $NaBH_4$ reduction of racemic *N*-(*o*-aryl)-5,5-dimethyl-2,4-oxazolidinediones (±)**1–6** to yield axially chiral hemiaminal type compounds, *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones **7–12**, having also a chiral center at C-4 which were found to racemize by a latent[10] ring-chain-ring tautomerization rather than by rotation around the N_{sp2}-C_{aryl} bond (see Fig. 1). The barriers to enantiomerization of the *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone enantiomers have been determined by either enantioselective HPLC by following the interconversion of one resolved enantiomer peak to the other or by temperature dependent ^1H NMR.

EXPERIMENTAL

General Methods

^1H and ^{13}C NMR spectra of all compounds were recorded on a Varian-Mercury VX-400 MHz-BB (30°C). IR analyses were performed on a Mattson Genesis II FTIR using KBr discs. Liquid chromatography analyses with UV detector (λ = 254 nm) were performed using CHIRALCEL OD-H column (particle size: 5 μm, column size: 250 × 4.6 mm^2), CHIRALPAK AD column (partical size: 5 μm, column size: 250 × 4.6 mm^2), CHIRALPAK IB column (partical size: 5 μm, column size: 250 × 4.6 mm^2) or CHIRAL-

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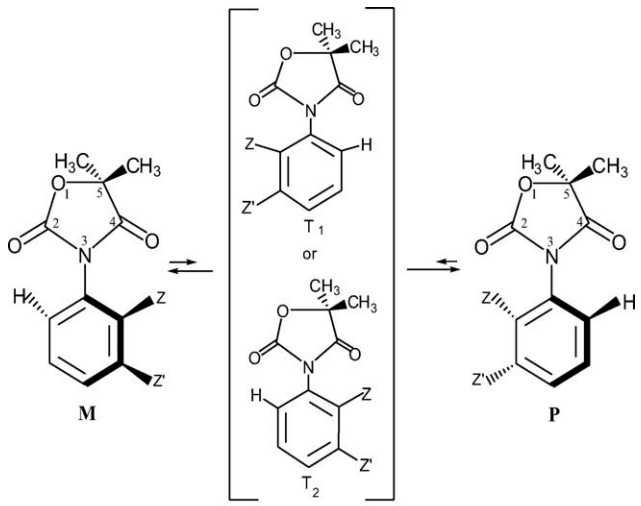


(±)**1**, Z= CH_3, Z'=H
(±)**2**, Z=Z'=benzo
(±)**3**, Z= F, Z'=H
(±)**4**, Z= Cl, Z'=H
(±)**5**, Z= Br, Z'=H
(±)**6**, Z= I, Z'=H

Scheme 1. The compounds subjected to reduction reaction by $NaBH_4$, T_1 and T_2 represent the transition states.

PAK IC column (partical size: 5 μm, column size: 250 × 4.6 mm^2). Separations were done at T = 280 K. Reactions were followed by TLC using silica gel 60-F_{254}. Elemental analyses were performed on Thermo Scientific Flash EA 1112 CHNS analyzer. Melting points were recorded using Electrothermal 9100 melting point apparatus.

Synthesis of Compounds (±)1–6

Compounds (±)**1–6**, *N*-(*o*-aryl)-5,5-dimethyl-2,4-oxazolidinediones were prepared according to the procedures given in Refs. [2] and [3].

Synthesis of Compounds 7–12

General procedure for the reduction reactions with sodium borohydride.[11] To a mixture of the starting material (1 eq) in THF was added a solution of sodium borohydride (4 eq.) in water at a rate to maintain the internal temperature at 20–25°C. The mixure was stirred at room temperature for 1–7 h, and the completion of the reaction was monitored by TLC. To the reaction mixture was added 2 M HCl (5 eq.) at a rate to maintain the internal temperature at 20–25°C. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and purified by ethyl acetate-hexane.

N-*(o-tolyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (7)*. The compound was prepared according to the general procedure using 1.00 g (4,56 mmole) compound (±)**1** in 14 ml THF (0,33 M), 0.69 g (18,25 mmole) sodium borohydride in 4,5 ml water (4,05 M). After extraction with ethyl acetate, the product was obtained as a white solid (1.00 g, 99%), mp 96-98°C (ethyl acetate-/*n*-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ 1.40 and 1.48 (6H, 2 × s, 2 × CH_3), 2.23 (3H, s, *o*—CH_3), 3.32 (1H, d, *J* 7.4, OH), 4.90 (1 H, d, *J* 7.4, C—H), 7.17–7.29 (4H, m, 4 × C—H); ^{13}C NMR (100 MHz; $CDCl_3$, Me_4Si): δ 151.8 (C = O), 132.9 (C), 130.2 (C), 127.4 (C—H), 125.4 (C—H), 124.9 (C—H), 123.1 (C—H), 84.3 (C—H), 78.8 (C), 22.9 (*o*—CH_3), 17.0 (CH_3), 14.3 (CH_3); elemental analysis: Found: C, 65.4; H, 7.1; N, 6.2; calculated for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3%; IR Data (ν_{max} (KBr)/cm^{-1}): 3262 (O—H), 1714 (C=O).

N-*(α-naphthyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (8)*. The compound was prepared according to the general procedure using 0.50 g (1.96 mmole) compound (±)**2** in 6 ml THF (0,33 M), 0.30 g (7.84 mmole) sodium borohydride in 1.8 ml water (4,35 M). After extraction with ethyl acetate, the product was obtained as a white solid (0.36 g, 71%), mp 124–126°C (ethyl acetate-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ1.48 and 1.64 (6H, 2×s, 2×CH_3), 3.80 (1H, br s, OH), 5.02 (1 H, s, C–H), 7.40–8.00 (7H, m, 7 × C—H); ^{13}C NMR (100 MHz; $CDCl_3$, Me_4Si): δ 156.3 (C=O), 134.8 (C), 131.5 (C), 130.9 (C), 129.4 (C—H), 128.9 (C—H), 127.5 (C—H), 127.3 (C—H), 126.7 (C—H), 125.8 (C—H), 122.4 (C—H), 88.5 (C—H), 82.9 (C), 27.2 (CH_3), 21.1 (CH_3); elemental analysis: Found: C, 70.1; H, 5.7; N, 5.7; calculated for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.4%; IR Data (ν_{max} (KBr)/cm^{-1}): 3337 (O—H), 1704 (C=O).

N-*(o-fluorophenyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (9)*. The compound was prepared according to the general procedure using 0.25 g (1.12 mmole) compound (±)**3** in 3.5 ml THF (0,32 M), 0.17 g (4.48 mmole) sodium borohydride in 1.1 ml water (4,00 M). After extraction with ethyl acetate, the product was obtained as a white solid (0.25 g, 65%), mp 85-86°C (ethyl acetate-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ 1.48 and 1.55 (6H, 2 × s, 2 × CH_3), 3.32 (1H, br s, OH), 5.15 (1 H, s, C—H), 7.16–7.57 (4H, m, 4 × C—H); ^{13}C NMR(100 MHz; toluene-d_8, Me_4Si): δ 155.3 (C=O), 130.3 (C—H), 129.0 (C), 127.4 (C), 124.3 (C—H), 116.2 (C—H), 115.9 (C—H), 88.0 (C—H), 82.8 (C), 25.8 (CH_3), 20.2 (CH_3); elemental analysis: Found: C, 58.4; H, 5.3; N, 6.4; calculated for $C_{11}H_{12}NO_3F$: C, 58.7; H, 5.4; N, 6.2%; %; IR Data (ν_{max} (KBr)/cm^{-1}): 3367 (O—H), 1752 (C=O).

N-*(o-chlorophenyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (10)*. The compound was prepared according to the general procedure using 0.20 g (0.84 mmole) compound (±)**4** in 2.6 ml THF (0,32 M), 0.13 g (3.34 mmole) sodium borohydride in 0,8 ml water (4,00 M). After extraction with ethyl acetate, the product was obtained as a white solid (0.19 g, 93%), mp 110–112°C (ethyl acetate-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ 1.40 and 1.53 (6H, 2 × s, 2 × CH_3), 3.63 (1H, br s, OH), 5.04 (1 H, s, C—H), 7.22–7.46 (4H, m, 4×C—H); ^{13}C NMR(100 MHz; $CDCl_3$, Me_4Si): δ 156.0 (C=O), 133.0 (C), 132.7 (C), 131.9 (C—H), 130.4 (C—H), 130.0 (C—H), 127.9 (C—H), 87.7 (C—H), 83.9 (C), 26.6 (CH_3), 20.9 (CH_3); elemental analysis: Found: C, 54.4; H, 5.0; N, 5.6; calculated for $C_{11}H_{12}NO_3Cl$: C, 54.7; H, 5.0; N, 5.8%); IR Data (ν_{max} (KBr)/cm^{-1}): 3338 (O—H), 1708 (C=O).

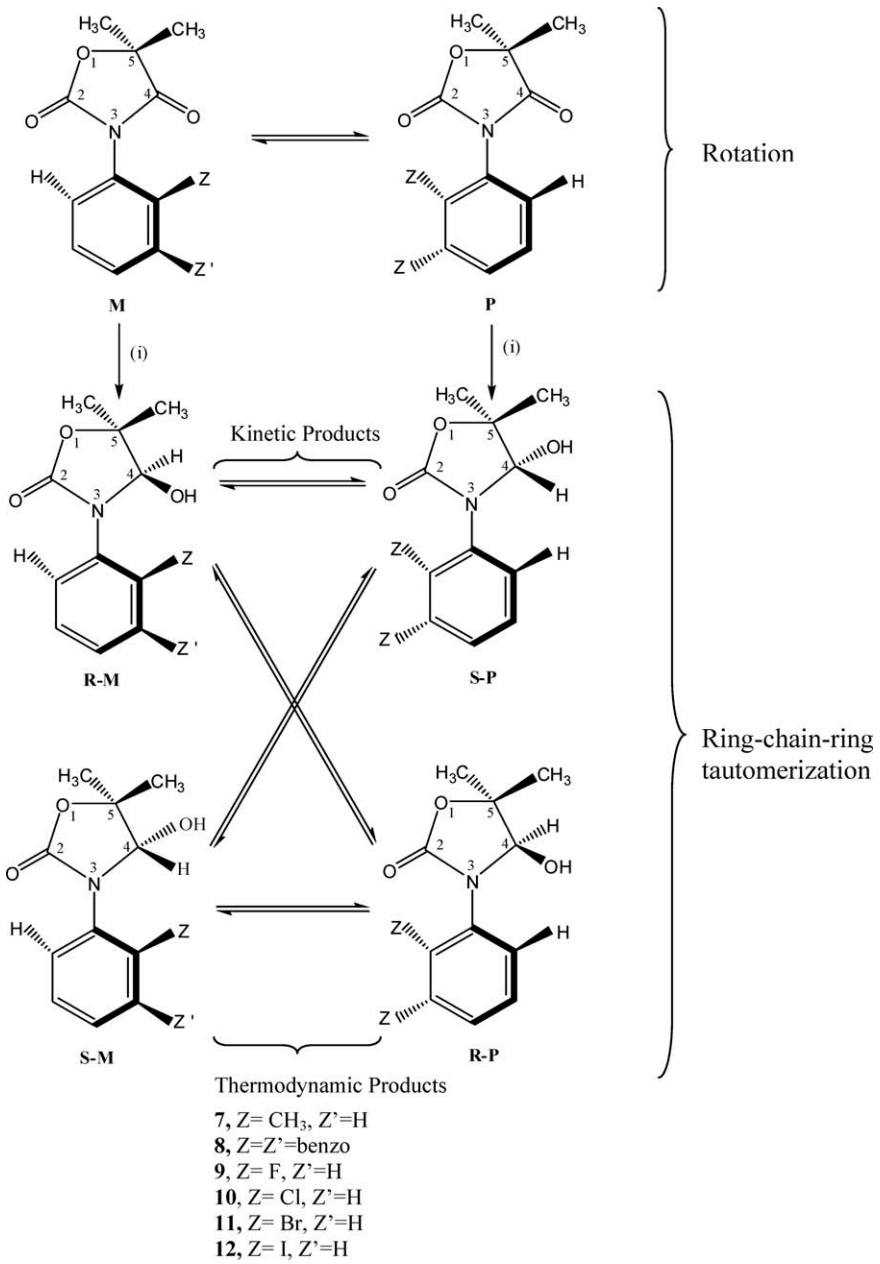


Fig. 1. The reaction of compounds (±)**1-6** with $NaBH_4$, (i) $NaBH_4$, THF-H_2O, room temperature. The reaction yielded the thermodynamic product by 100% diastereoselectivity.

N-*(o-bromophenyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (11)*. The compound was prepared according to the general procedure using 0.30 g (1.06 mmole) compound (±)**5** in 3.5 ml THF (0,30 M), 0.16 g (4.22 mmole) sodium borohydride in 1.0 ml water (4,22 M). After extraction with ethyl acetate, the product was obtained as a white solid (0.24 g, 79%), mp 154–156°C (ethyl acetate-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ1.42 and 1.56 (6H, 2 × s, 2 × CH_3), 3.42 (1H, d, *J* 8.0, OH), 5.09 (1 H, d, *J* 8.0, C—H), 7.16–7.60 (4H, m, 4 × C—H); ^{13}C NMR(100 MHz; $CDCl_3$, Me_4Si): δ 155.6 (C=O), 134.2 (C), 133.6 (C—H), 132.2 (C—H), 130.3 (C—H), 128.6 (C—H), 123.4 (C), 87.5 (C—H), 83.5 (C), 26.7 (CH_3), 21.0 (CH_3); elemental analysis: Found: C, 45.8; H, 4.3; N, 5.1; calculated for $C_{11}H_{12}NO_3Br$ C, 46.1; H, 4.2; N, 4.9%; IR Data (ν_{max} (KBr)/cm^{-1}): 3342 (O—H), 1708 (C=O).

N-*(o-iodophenyl)-4-hydroxy-5,5-dimethyl-2-oxazolidinone (12)*. The compound was prepared according to the general procedure using 0.20 g (0.60 mmole) compound (±)**6** in 1.9 ml THF (0,32 M), 0.091 g (2.42 mmole) sodium borohydride in 0.6 ml water (4,00 M). After extraction with ethyl acetate, the product was obtained as a white solid (0.13 g, 66%), mp 148–150°C (ethyl acetate-hexane); ^{1}H NMR (400 MHz; $CDCl_3$, Me_4Si): δ 1.50 and 1.69

TABLE 1. Reduction of compounds (±)1–6 by $NaBH_4$

Starting materials	Product no	Yield (%)	Reduction time[a]
(±)**1**	**7**	99	3 h 30 min
(±)**2**	**8**	71	7 h
(±)**3**	**9**	65	4 h
(±)**4**	**10**	93	4 h 30 min
(±)**5**	**11**	79	4 h 30 min
(±)**6**	**12**	66	6 h 30 min

[a]Reduction times were determined by following the reaction with TLC using chloroform or ethylacetate: *n*-hexane mixture (1:2) as an eluent. Samples were taken at 30 min intervals.

(6H, 2 × s, 2 × CH_3), 3.36 (1H, d, *J* 7.0, OH), 5.16 (1 H, d, *J* 7.0, C—H), 7.08–7.93 (4H, m, 4 × C–H); ^{13}C NMR(100 MHz; $CDCl_3$, Me_4Si): δ_C 155.6 (C=O), 140.0 (C—H), 137.3 (C), 131.9 (C—H), 130.6 (C—H), 129.6 (C—H), 99.3 (C), 87.5 (C—H), 83.6 (C), 27.0 (CH_3), 21.2 (CH_3) ; elemental analysis: Found: C, 39.5; H, 3.8; N, 4.3; calculated for $C_{11}H_{12}NO_3I$: C, 39.7; H, 3.6; N, 4.2%); IR Data (ν_{max} (KBr)/cm^{-1}): 3334 (O—H), 1709 (C=O).

RESULTS AND DISCUSSION

Reaction with $NaBH_4$[11]

The reduction reactions of compounds (±)**1–6** were carried out by four molecular equivalents of $NaBH_4$ in THF. It was observed that the reaction took place regioselectively reducing only the C-4 carbonyl and not the C-2, to yield *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones with 100% diastereoselectivity (compounds **7–12**) (Fig. 1, Table 1). The ring structures of compounds **7–12** were determined by ^{1}H and ^{13}C NMR in $CDCl_3$ (see Fig. 2).

A second hydride transfer that would result in ring opening did not take place probably due to the steric hindrance of the 5,5-dimethyl groups.

The ^{1}H NMR spectra of the hemiaminals **7–12** showed diastereotopic splittings for the C-5 methyl groups like the precursor compounds (±)**1–6** which have been discussed previously in detail.[2,3] Because of the formation of a chiral center on C-4 in compounds **7–12**, in addition to the chiral axis, the chemical shift difference between the diastereotopic geminal dimethyl protons for these compounds were found to increase by 0.06 ppm compared with those of (±)**1–6**.

Stereoselectivity (Diastereoselectivity) in Reduction of Compounds (±)1–6

The reaction of $NaBH_4$ with compounds (±)**1–6** can in principle be expected to form four stereoisomers due to the formation of a new chiral center on C-4: two enantiomeric (*S-M/R-P, S-P/R-M*) and two diastereomeric pairs (*S-M/S-P, R-M/R-P*) (see Fig. 1). However the ^{1}H and ^{13}C NMR of the reduction products **7–12** showed the presence of only one of these diastereomeric pairs (*S-M/R-P* pair as has been proved by NOESY and will be explained later in the text) (see Fig. 2) and the enantioselective HPLC on the columns Chiralcel OD-H, Chiralpak AD-H, IB and/or IC showed only one enantiomeric pair.

The observation of only one enantiomeric pair for compounds **7–12** led us consider the possibility of a stereoselective reduction. As boron in $NaBH_4$ is tetracoordinated, in the attack of the hydride, the Felkin-Anh model is usually invoked.[5] The attack of the hydride takes place *anti* to

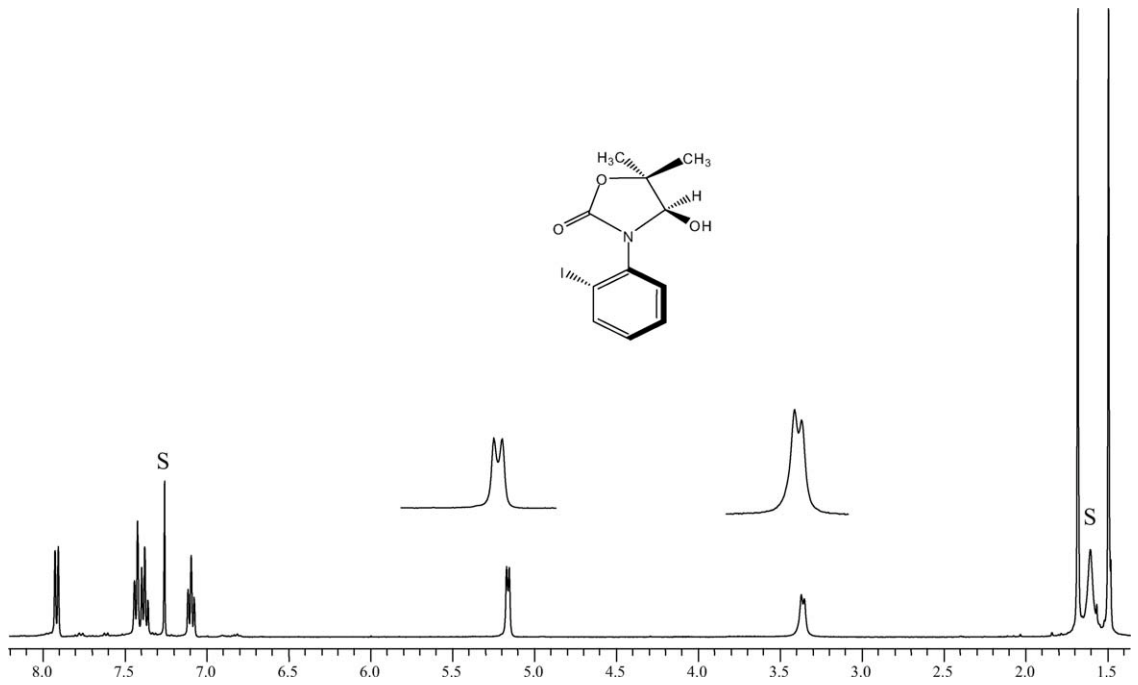


Fig. 2. 400 MHz ^{1}H NMR spectrum of compound **12** in $CDCl_3$. S:Solvent.

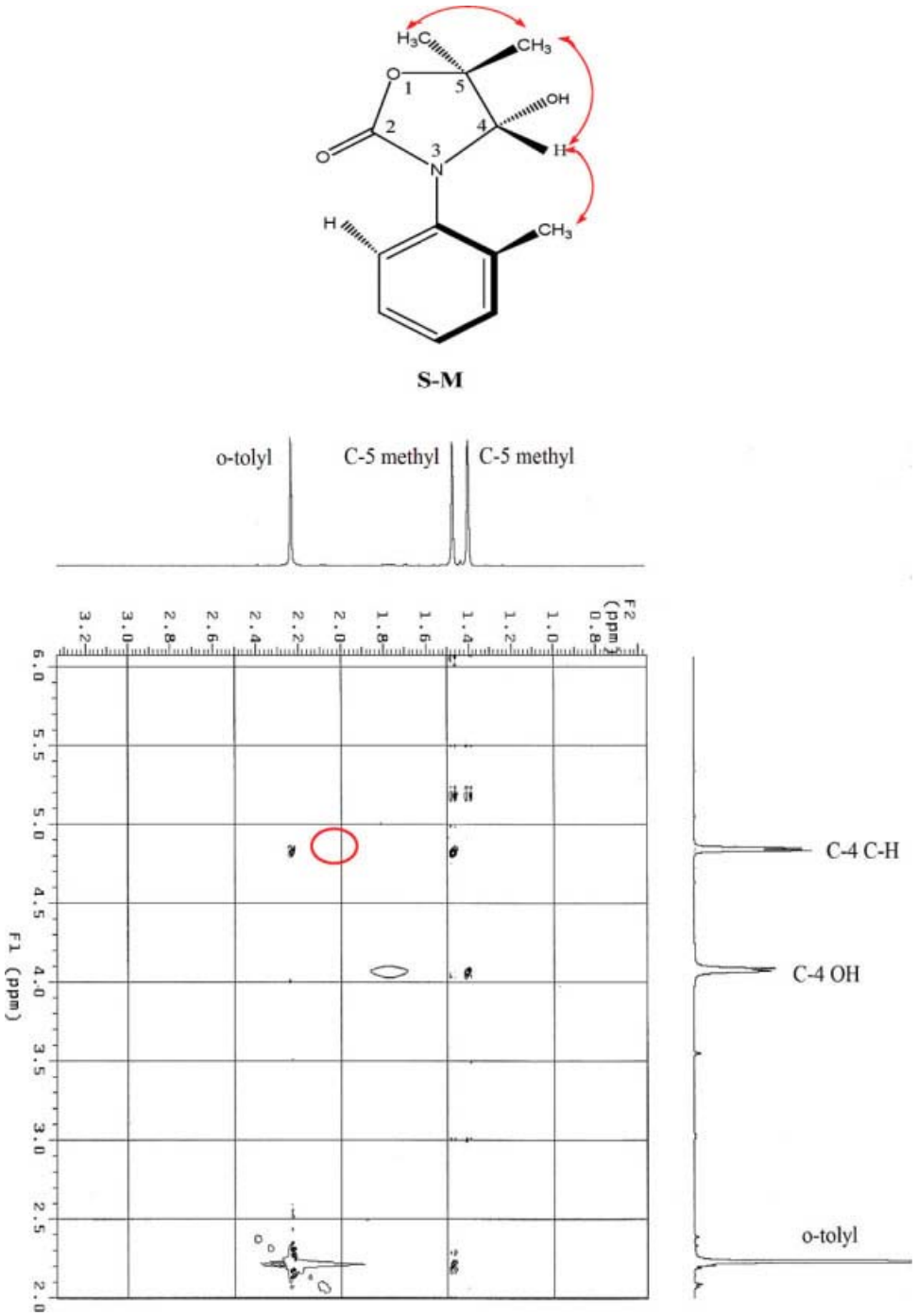


Fig. 3. The NOESY spectrum of compound **7** in $CDCl_3$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the most bulky or the polar group, i.e., the *ortho* substituent in our case, resulting in a facial selectivity for the carbonyl group. Thus, the attack of a hydride on prochiral C-4 carbonyl group can be accomplished either on the *Re* or *Si* face of the carbonyl. Because of the presence of an *ortho* substituent that is very close to the reaction site, a selectivity for the attack from the opposite side of the *ortho* substituent could be expected. However, this would form quite unstable products where the hydroxyl and the *ortho* substituents are *syn* with respect to each other (kinetic products) (see Fig. 1).

NOESY spectra for compounds **7** and **12** were taken to elucidate the stereochemistry of the reduction products (Figs. 3 and 4). The observed crosspeaks between the C-4 carbinyl hydrogen and the *ortho* methyl protons of compound **7** revealed that these protons are on the same side,

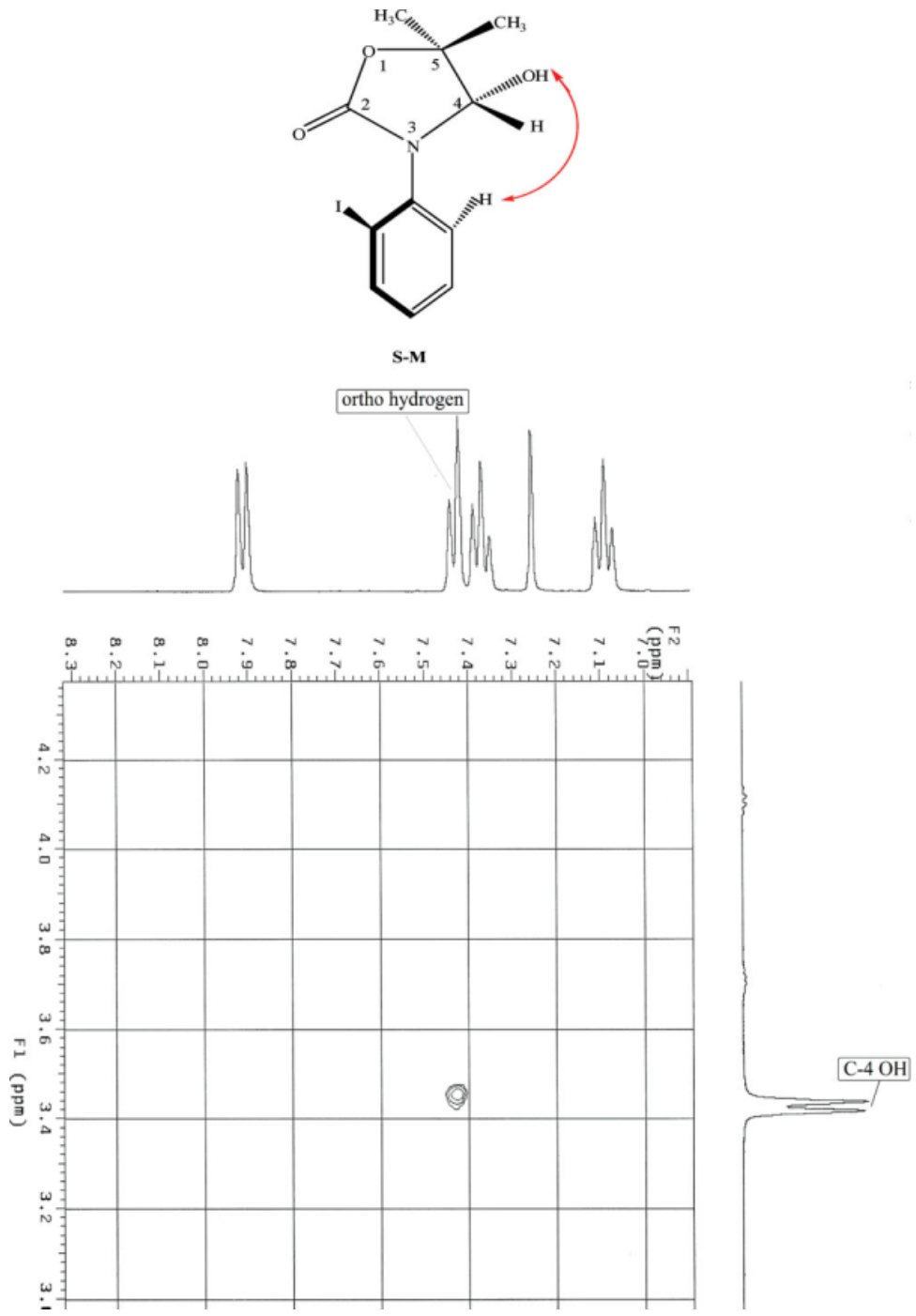
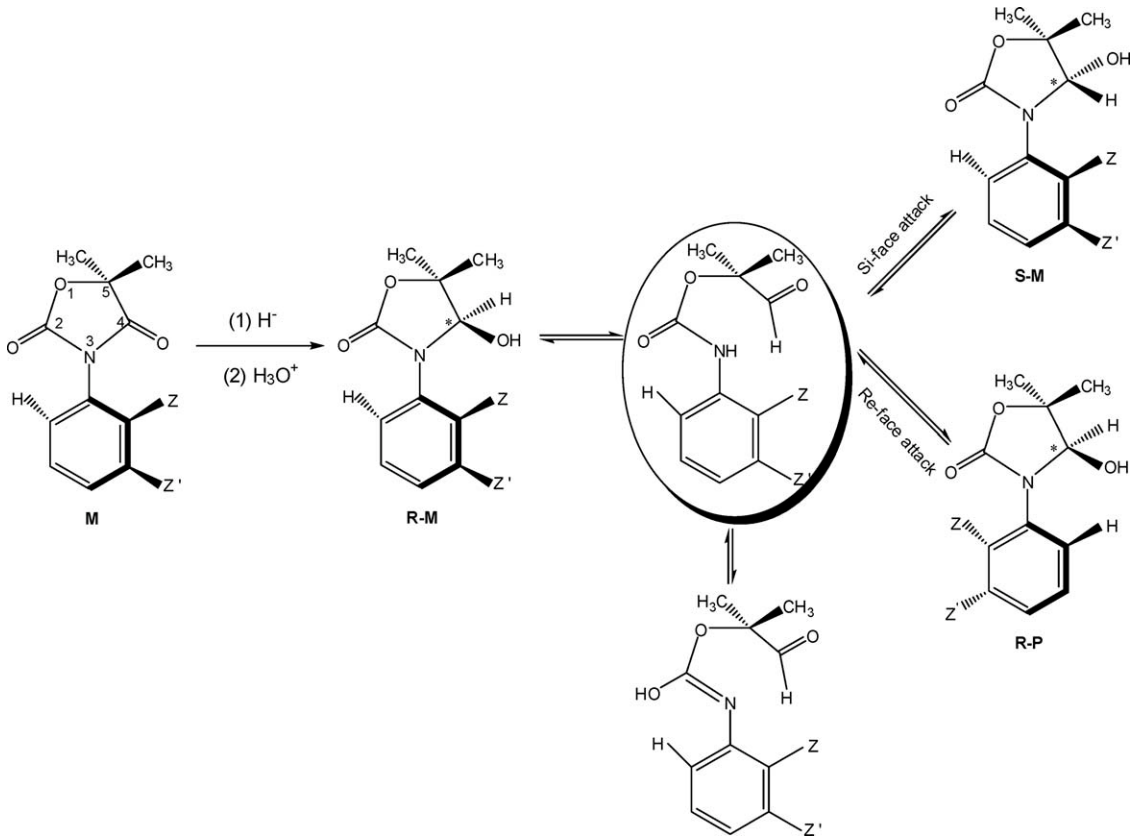


Fig. 4. The NOESY spectrum of compound **12** in $CDCl_3$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

indicating that they are the thermodynamic products, (*S-M*) and (*R-P*) (see Fig. 3). The spatial proximity between the carbinyl hydrogen and one of the C-5 methyl groups could also be seen in this spectrum. In the NOESY spectrum of compound **12** (see Fig. 4), the crosspeak observed between *ortho* hydrogen and C-4 hydroxyl group also showed that the isomers have conformations where C-4 hydroxyl group and iodine atom are on opposite sides (Thermodynamic products, (*S-M*) and (*R-P*)).

Ring-Chain-Ring Tautomerism: Mechanism and Kinetics of the Interconversion Between the N*-(*o*-aryl)-4-Hydroxy-5,5-dimethyl-2-oxazolidinone Enantiomers, (7–12) (*S-M↔R-P/R-M↔S-P*)*

Ring-chain tautomerization has been shown to occur in a number of heterocyclic compounds.[10,12–20] The tautomerism results from an interconversion of the chain and the ring isomers.



Scheme 2. Racemization of compounds **7–12** through an aldehyde intermediate.

For compounds **7–12**, the two enantiomers (*S-M*) and (*R-P*) (see Fig. 1) were found to be resovable by chiral chromatography and the separated enantiomer was found to thermally interconvert to its counterpart with time and finally racemized. This fact pointed to a ring-chain-ring tautomerization where the hemiaminal[7–12] opened to give the corresponding aldehyde (Scheme 2) which then reclosed by either a *Re* or *Si* face attack of the nitrogen to give (*S-M*) and (*R-P*) products.

To clarify the mechanism of enantiomerization between the enantiomeric pairs (*S-M/R-P* pair), one of the enantiomers of compounds **7–12** was collected micropreparatively by HPLC using a chiral column (Table 2). The ethanol solution of the collected enantiomer was kept at 30°C,[10–12] at 50°C (**7, 8**) or at 78°C (**9**) in a constant temperature bath and its interconversion to the other enantiomer was followed by taking an aliquot of ethanol solution at certain time intervals and analyzing them by HPLC. Considering the interconversion follows a first order reaction kinetics, the slope of the line ln ([enantiomer]$_t$- 50/ [enantiomer]$_0$-50) = -2 kt, where [enantiomer]$_t$ is the per cent composition of an enantiomer at time t, [enantiomer]$_0$ is the starting per cent composition of the enantiomer and 50 is the equilibrium composition,[21] gave the rate constant (see Fig. 5) and hence the activation barrier for interconversion.[21] The kinetic and chromatographic data pertinent to enantiomerizations are given in Table 2.

Having in hand the enantiomerization barriers for compounds **7–12**, we could clearly see that the barriers for the *ortho*-fluoro, chloro, bromo and iodo derivatives did not show a linearity depending on the size of the *ortho*-substituent (Fig. 6a). The barriers to rotation for the *ortho*-fluoro, chloro, bromo and iodo derivatives of the corresponding oxazolidinediones [(±)**1–6**] on the other hand where the enantiomerization was due to the hindered rotation[2] around the N_{sp2}-C_{aryl} bond did show a linearity depending on the *o*-halogen substituent (Fig. 6b).[2] This was taken as a proof for the existence of a different mechanism for the enantiomerization for these compounds. Previously a ring opening-ring closure mechanism has been proposed for six-membered N-*o*-aryl substituted heterocyclic compounds.[22]

The interconversion of (*S-M*) to (*R-P*) for compounds **7–12** could proceed via an aldehyde intermediate formed from a ring cleavage (Scheme 2) as has been observed for structurally related compounds.[23,24] However, such an intermediate was not observed in the NMR time scale in $CDCl_3$. Taking the NMR spectra in d_6-DMSO in the absence or presence of trifluoroacetic acid-*d* or pyridine-d_5, which could stabilize the aldehyde intermediate[10,12] did not exhibit its existence as well. With the aim of trapping the aldehyde intermediate as an imine, the compound **10** was treated with benzyl amine in toluene under reflux for one day as has been described in Ref. 10. Analysis of the

TABLE 2. The kinetic and chromatographic data for racemization of compounds 7-12, determined by HPLC

Entries	Column	Eluent composition (% v, *n*-Hexane: % v, Ethanol)	Flow Rate/ml min^{-1}	Capacity Factors, k_1&k_2	Selectivity, α	Rate Constant, k/sec^{-1}	Activation Barrier, $\Delta G^{\#}$/kJ mol^{-1}	$t_{1/2}$/min (303 K)
7	Chiralpak IB	90:10	0.7	2.33 2.53	1.09	5.00×10^{-5}[a]	105.92 ± 0.7	–[b]
8	Chiralcel OD-H	80:20	0.4	1.19 1.91	1.61	1.67×10^{-5}[a]	108.86 ± 0.7	–[c]
9	Chiralpak IB	95:5	0.6	3.18 3.89	1.22	5.75×10^{-5}[d]	114.94 ± 0.7	–[e]
10	Chiralpak IB	90:10	0.7	2.09 2.36	1.13	8.00×10^{-5}[f]	98.02 ± 0.7	72
11	Chiralcel OD-H	90:10	0.6	1.53 2.08	1.36	1.53×10^{-4}[f]	96.38 ± 0.7	42
12	Chiralcel OD-H	90:10	0.6	1.89 3.11	1.65	1.58×10^{-4}[f]	96.30 ± 0.7	36

[a]At 50 ± 2°C.
[b]The interconversion was too slow at 303 K to determine the kinetics (3% interconversion in 100 min at 313 K).
[c]The interconversion was too slow at 303 K to determine the kinetics (2% interconversion in 106 min at 313 K).
[d]At 78 ± 2°C.
[e]The interconversion did not take place at 303 K.
[f]At 30 ± 2°C.

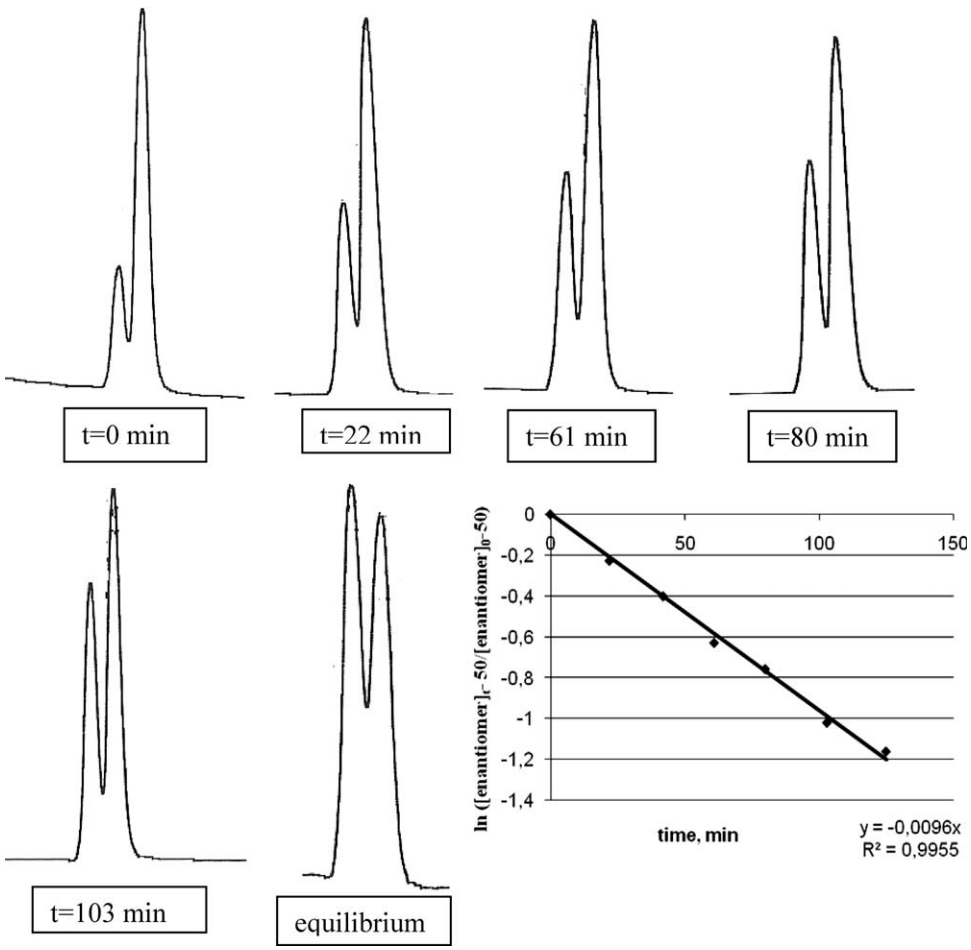


Fig. 5. The HPLC chromatograms taken to follow the racemization and the plot of ln ([enantiomer]$_t$- 50/[enantiomer]$_0$-50) versus time (min) at 30°C for compound **10**.

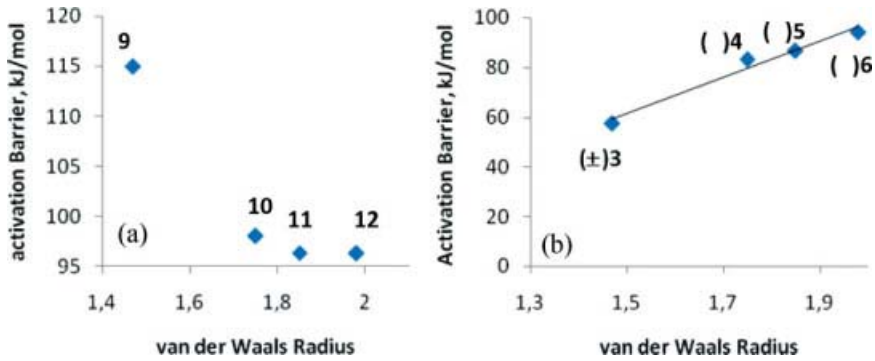
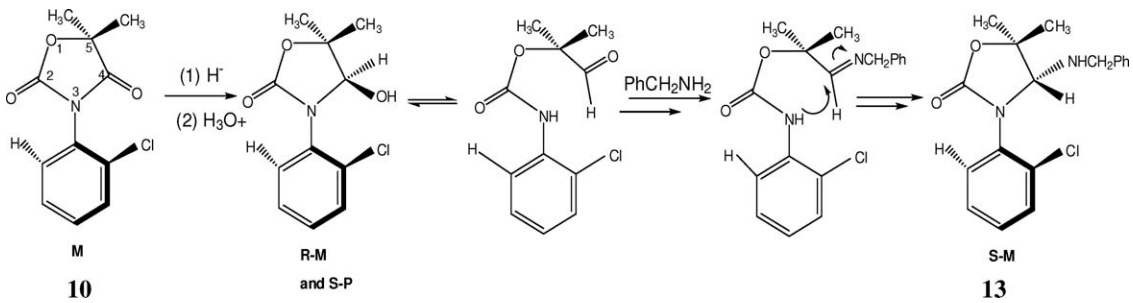


Fig. 6. The dependance of the enantiomerization barriers on the van der Waal's radius of the ortho substituents (**a**) for compounds **9–12** (**b**) for compounds **3–6**.[2] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

^{1}H and ^{13}C NMR spectra of the crude product from this reaction showed the presence of a cyclic aminal structure (**13**) formed probably by an attack of NH to the formed imine (Scheme 3, Fig. 7). This was taken as a proof that the enantiomerization took place through an aldehyde intermediate.

Comparison of the activation barriers for enantiomerization for compounds **7–12** (Table 2) revealed that the *ortho* substituents had an effect on the rate of tautomerization as has been observed before.[25,26] It is known that electron donating groups on phenyl ring favors the ring formation, whereas the electron withdrawing groups leads to the formation of open chain.[12,13] After the attack of an hydride to the C-4 carbonyl selectively to form the (*R-M*) and (*S-P*) isomers (Scheme 2), the formed hydroxy lactam might turn into an aldehyde via ring opening due to the steric interference caused by the *syn*-orientation of the hydroxyl and Z groups. In fact, the unstable (*R-M*) isomer could be stabilized by two ways: first, by the rotation around the chiral axis or second by ring opening. The most important factor that results in ring opening is that during rotation, the *ortho* substituents orient the lone pair electrons on oxygen towards the C-4 carbonyl, assiting the formation of an aldehyde. After ring opening, either due to the gem-dimethyl effect (Thorpe-Ingold effect),[27] and/or the nucleophilicity of N, the molecule favors the intramolecular cyclization as the two reacting sites are close to each other (Compounds **7–12**). The fact that the rate of enantiomerization increases from fluorine to iodine derivatives could also be explained by the increased nucleophilicity of the N in this series (Scheme 2).[12,13] It has been observed that, the rate of enantiomerization for compounds **9–12** depended on both the nature of the *ortho* substituent and its size (Table 2). As can be seen from Table 2 compound **12** has the highest enantiomerization rate. This fact was attributed to the large van der Waals radius of iodine that caused a more rapid ring opening than the other halogen *ortho* substituents. Also because of the lowest electronegativity of iodine atom compared with the other halogens an increase in the nucleophilicity of the N can be expected. Thus the hemiaminal ring **12** could more rapidly open and then close compared with **9–11**. Because of the smallest van der Waals radius of florine atom, at 30°C compound **9** could not form an aldehyde intermediate as will be explained further in the text.

The ^{1}H NMR spectrum of compound **9** although showed the presence of only one diastereomer at 30°C, when the toluene-d_8 solution of the compound was cooled from 30°C to −70°C in the NMR probe (see Fig. 8) the other diastereomer appeared at −53°C. Also, it was observed that the chemical shift of the hydroxyl proton was deshielded remarkably from approximately 3.7 to 6.1 ppm revealing that there was a hydrogen bonding[2,3] between the hydroxyl hydrogen and the fluorine atom. The appearance of the other isomer at −53°C was attributed to a slow rotation around the C—N bond axis. Therefore, it was concluded that the rotation around the C—N single bond of compound **9** was so fast at room temperature making the resulting isomers enantiomeric having only (*S*) and (*R*) configurations on C-4. The existence of



Scheme 3. Trapping of the aldehyde intermediate of compound **10** as an aminal **13**.

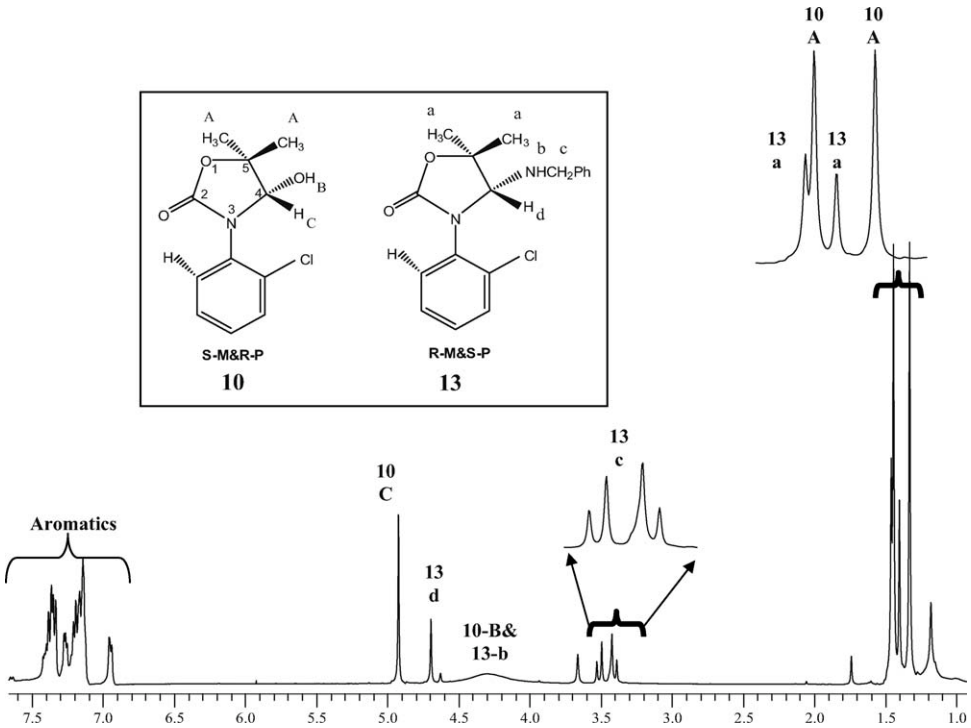


Fig. 7. The 400 MHz ^{1}H NMR spectrum of a crude product containing **10** and **13** in $CDCl_3$.

enantiomers was proven by the ^{1}H NMR spectrum of compound **9** in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoro ethanol (see Fig. 9), by observing splitting of the peaks due to the formation of diastereomeric association complexes.[2,3,28]

At temperatures below −50°C the hydroxy proton at C-4 can form a stronger hydrogen bond with *ortho* fluorine, yielding (*R-M*) and (*S-P*) enantiomers in addition to their diastereomers (*S-M*) and (*R-P*). The separation in Hertz between the signals of the diastereomers in the absence of rapid rotation could be achieved at −53°C (220 K) and found as 12 Hz for 400 MHz NMR instrument. The coalescence of the signals took place at −53°C (see Fig. 8). By using the Eyring Equation,[29] the activation barrier to hindered rotation was found as 47.3 ± 0.05 kJ/mol which was lower than that of compound (±)**3** (57.3 kJ/mol).[2] This decrease in the activation barrier was explained in terms of the stability of also the transition state of **9** during rotation via hydrogen bonding. As the hydroxyl and *ortho* fluorine groups are very close to each other in space in the transition state, they should be capable of forming a stronger hydrogen bond that will stabilize the transition state.

The enantiomers of compound **9** could be resolved by enantioselective HPLC on Chiralpak IC column at 7°C. Because of the absence of the *M* and *P* atropisomerism resulting from the fast rotation around the C—N single bond, the two chromatographic peaks observed were attributed to the (*R*) and (*S*) enantiomers of compound **9**. One of the enantiomers was resolved micropreparatively to determine the rate of its conversion to its counterpart. However their interconversion did not take place at 30°C, was too slow at 50°C and 65°C (2% decrease in concentration after 138 min at 50°C, 4.4% decrease in concentration after 136 min at 65°C), and could only be followed at 78°C. This observation proved the importance of the magnitude of the van der Waals radius on tautomerization assisting the ring opening and formation of an aldehyde intermediate. Because of the smallest van der Waals radius of fluorine and the lowest nucleophilicty of N carrying the *o*-fluorophenyl, ring opening and closure was difficult resulting in a highest activation barrier in the series (Table 2).

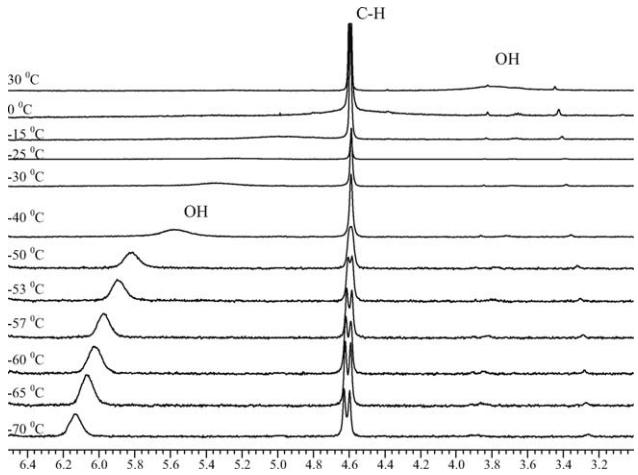


Fig. 8. 400 MHz low temperature dynamic NMR study of compound **9** in toluene-d_8.

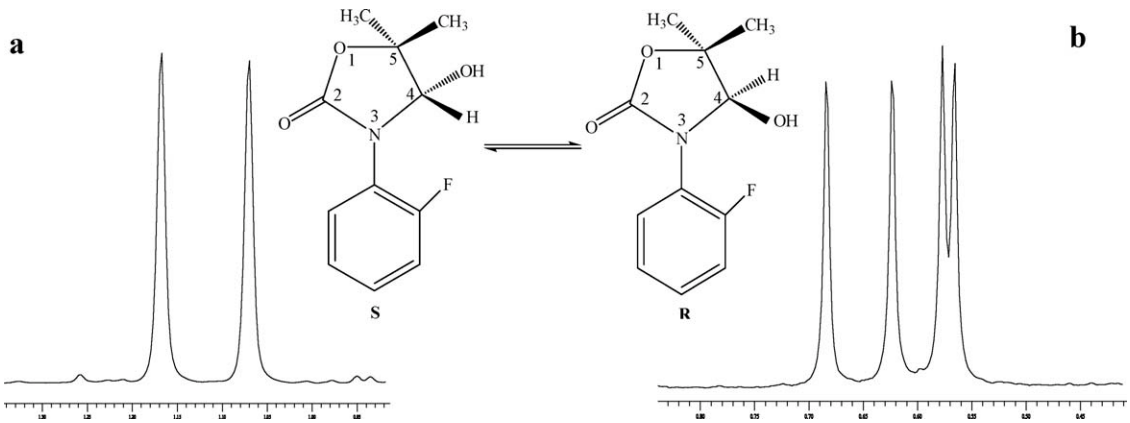


Fig. 9. Part of the ^{1}H NMR spectrum of compound **9** showing the signals of diastereotopic methyl protons on C-5 in the (**a**) absence and (**b**) presence of chiral auxiliary (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluro ethanol.

The tolyl and naphthyl derivatives (**7** and **8**) opened very slowly at 30°C as revealed by the fact that the resolved enantiomer interconverted to its counterpart only by 3% in 100 min and by 2% in 106 min, at 40°C for **7** and **8**, respectively. At 50°C, however, the oxazolidinone ring of **7** and **8** opened because high temperatures generally

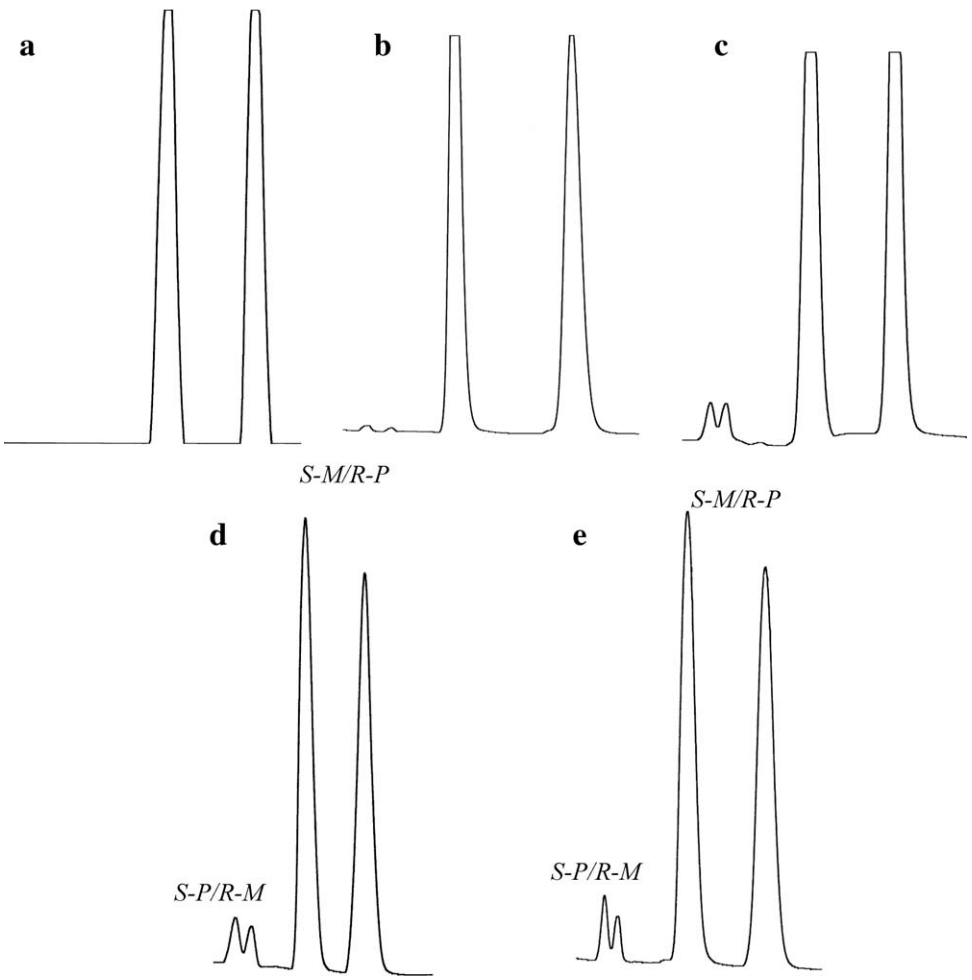
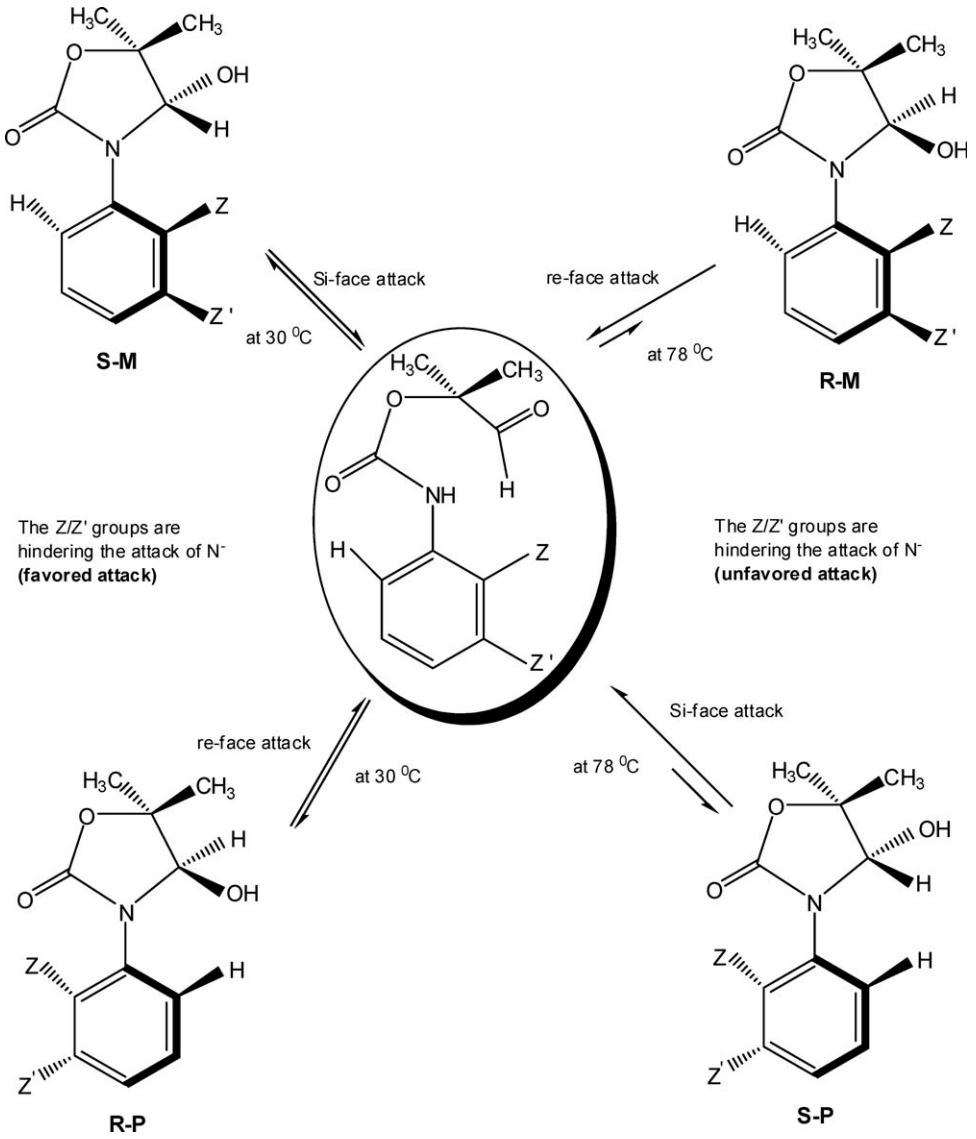


Fig. 10. The chromatograms taken to follow the thermal equilibration of the diastereomeric rotational isomers of **12**, (**a**) t = 0 min, (**b**) t = 97 min, (**c**) t = 2117 min, (**d**) t = 5451 min, (**e**) t = 6332 min (equilibrium), column: Chiralcel OD-H, eluent: 90%:10% (*n*-hexane:ethanol, v/v), Flow: 0.5 ml/min, λ: 254 nm, α: 1.29 and 1.87 for the minor and major enantiomeric pairs, respectively.



Scheme 4. Interconversion of enantiomeric and diastereomeric isomers of *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones **7–12** through an aldehyde intermediate.

favor the formation of the open chain,[12] and then, due to the higher nucleophilicity of N, together with the gem-dimethyl effect the ring was reformed immediately.

MECHANISM OF THE INTERCONVERSION BETWEEN THE DIASTEREOMERIC *N*-(*O*-ARYL)-4-HYDROXY-5,5-DIMETHYL-2-OXAZOLIDINONES (7–12) (S-M↔S-P/R-P↔R-M)

When the product **12** (Fig. 10a) was injected to the Chiralcel OD-H column only two isomers (50% each) which were interpreted as enantiomers of each other, were detected. However, after keeping the solution of **12** at 78°C for 97 min the other pair, minor in amount (Fig. 9b) could be observed. Equilibrium for this interconversion was reached after 6332 min at 78°C (Fig. 9e) having a ratio of 94.09%:5.91%. The observation of the newly formed enantiomeric pair in small amount revealed that they were the (*S-P*) and (*R-M*), the initial kinetic products. It was proved that the hemiaminal ring opens and tautomerizes through an aldehyde intermediate (Scheme 2), and the N in the aldehyde form favors the less hindered attack to form more stable isomers (*S-M*) and (*R-P*) at 30°C. However, at higher temperatures (78°C) sufficient energy could have been supplied for the attack of N from the other side to form the less stable (*S-P*) and (*R-M*) isomers (Scheme 4). Therefore upon reflux at 78°C in ethanol, the expected four isomers could be observed. The equilibrium compositions of the diastereomeric pairs for compounds **7–12** are given in Table 3.

The diastereomer ratios given in Table 3 revealed the importance of the size of the *ortho* substituents also on the diastereomer interconversion and thus the steric interference between the groups on N and the site to be attacked.

TABLE 3. The equilibrium compositions of diastereomers of compounds 7-12

Entries	Column	Eluent composition, v/v (*n*-hexane%:ethanol%)	Flow Rate/ ml min^{-1}	Diastereomer ratio at equilibrium (*S-M*/*R-P*%:*R-M*/*S-P*%)
7[a]	Chiralpak IB	90:10	0.7	90.1:9.9
8[a]	Chiralcel OD-H	70:30	0.3	94.8:5.2
9[b]	–	–	–	50:50
10[a]	Chiralpak IB	90:10	0.7	68.0:32.0
11[a]	Chiralcel OD-H	90:10	0.5	94.5:5.5
12[a]	Chiralcel OD-H	90:10	0.5	94.1:5.9

[a]The diastereomer interconversion was done at 78°C and followed by chiral HPLC.
[b]The diastereomer interconversion was followed by temperature dependent NMR.

As chlorine (compound **10**) has a smaller van der Waals radius than bromine and iodine in the halogen series, the attack of N is less hindered compared to other attacks, forming the less stable isomers in relatively higher equilibrium amounts (Table 3). The fixed orientation of the peri hydrogen of the α-naphthyl for compound **8**, probably causes a similar steric requirement as the iodo substituent in compound **12** to hinder the attack of N to the *Re* face. The attack of N carrying an *o*-tolyl should also be hindered because of the relatively large van der Waals radius of the methyl group. However, because of the flexibility of methyl, the unstable (*S-P*)/(*R-M*) isomers were produced in greater equilibrium amounts compared to the naphtyl derivative.

The diastereomeric interconversion for compound **9** does not take place *via* ring opening-ring closure mechanism, but due to rotation around the C—N single bond due to the small size of the fluorine atom. The observation of two diastereomers upon cooling was attributed to the hindered rotation around the C—N single bond at lower temperatures (−53°C) in the hemiaminal structure (see Fig. 8) and the hydrogen bonding between *ortho*-fluorine and C-4 hydroxyl group. The diastereomeric 1:1 ratio obtained by the integration of the ^{1}H NMR signals at around 4,6 ppm (see Fig. 8), results from the equal stability of the two diastereomers.

CONCLUSIONS

The $NaBH_4$ reduction of *N*-(*o*-aryl)-5,5-dimethyl-2,4-oxazolidinedione ring to yield *N*-(*o*-aryl)-4-hydroxy-5,5-dimethyl-2-oxazolidinones has been found to take place diastereoselectively yielding the thermodynamically stable (*S-M*) and (*R-P*) isomers whose absolute conformations were found by NOESY experiments. The interconversion of enantiomeric hemiaminals ((*S-M*) and (*R-P*) isomers) was found to proceed through an aldehyde intermediate formed from a ring cleavage *via* a ring-chain-ring tautomerization. It was found that the rate of tautomerization depended on the steric bulkiness assisting the ring opening (or formation of an aldehyde intermediate) and also on the electron donating or withdrawing ability of the *ortho* substituent causing the ring closure of the aldehyde intermediate. In the halogen series, due to the lowest electron withdrawing property and the highest steric impediment, the activation barrier of iodine derivative was found to be the lowest one. The interconversion between diastereomeric hemiaminals (interconversion of (*S-M*)/(*R-P*) to (*R-M*)/(*S-P*)) took place at higher temperatures (78°C) and was found to be affected by the size of the *ortho* substituents.

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