

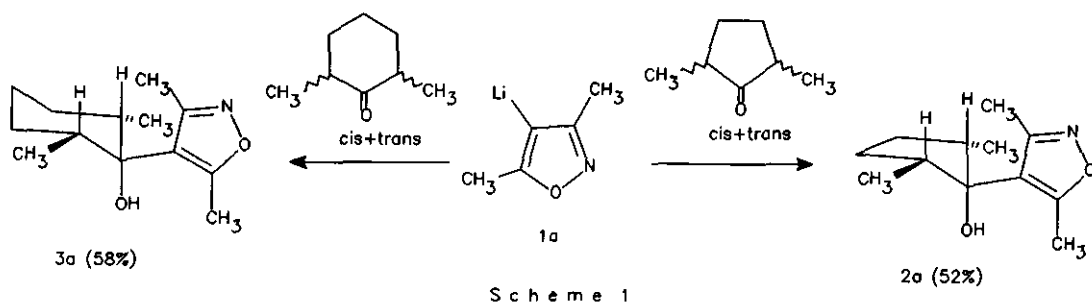
DIASTEREOSELECTIVITY IN THE REACTION OF 3-METHYL-5-(METHYL- OR PHENYL)ISOXAZOL-4-YLLITHIUM AND α,α' -DIMETHYLCYCLOALKANONES

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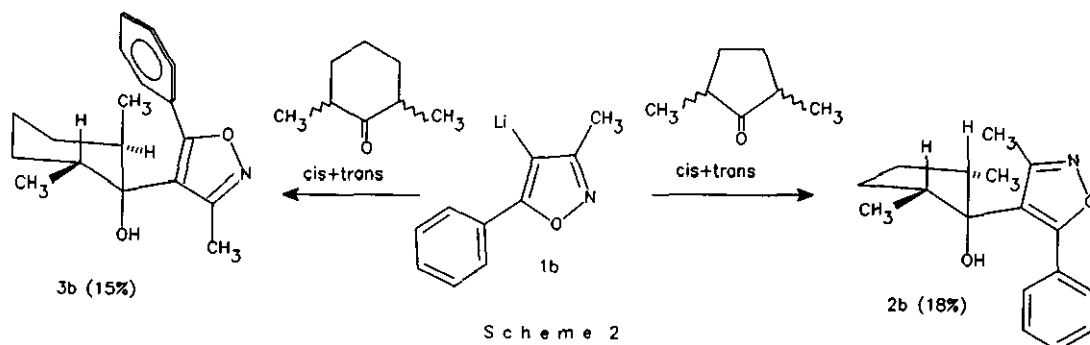
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Abstract — Addition of 3-methyl-4-lithio-5-(methyl- or phenyl)isoxazoles to stereoisomeric mixtures of α,α' -dimethylcycloalkanones afforded meso 1S^{*},2R^{*}, (5 or 6)S^{*}-2, (5 or 6)-dimethyl-1-[3'-methyl-5'-(methyl- or phenyl)isoxazol-4'-yl]cycloalkan-1-ols. In one case none of meso form, but only the racemic 2,6-dimethyl-1-(3'-methyl-5'-phenylisoxazol-4'-yl)cyclohexan-1-ol was obtained. This compound showed restricted rotation phenomena at room temperature.

Isoxazole chemistry is an important tool for organic synthesis of natural products¹ and heterocyclic systems.² Asymmetric synthesis through isoxazolines³ and isoxazoles⁴ is yet an useful way to selective construction of carbon skeletons. With this in mind, we are searching selective methods⁵ in isoxazole chemistry which could be useful in organic synthesis. In this paper we report the diastereoselective addition of 3,5-dimethylisoxazol-4-ylolithium and 3-methyl-5-phenylisoxazol-4-ylolithium to commercial mixtures of cis- and trans- isomers of 2,5-dimethylcyclopentanone and 2,6-dimethylcyclohexanone, affording diastereoisomers of the possible addition products in all cases studied. Thus when an ethereal solution of 3,5-dimethylisoxazol-4-ylolithium (**1a**) was treated with a commercial mixture of cis- and trans-isomers of 2,5-dimethylcyclopentanone or 2,6-dimethylcyclohexanone, followed by hydrolysis and separation of product on column chromatography, one of the symmetric meso-forms of the corresponding cycloalkanols were recovered in each case. Products of reactions were the isoxazolic cycloalkanols (**2a**) and (**3a**). Yields of reaction were 52-58%, which can be regarded as fair yields by considering that only the cis-diequatorial cyclic ketone reacted with isoxazole (**1a**) in both cases reported. Reaction products for **1a** and obtained yields are shown in Scheme 1. ¹H- and ¹³C-nmr spectra of **2a** and **3a** showed a single signal (one doublet in ¹H-nmr) corresponding to the methyl groups bonded to the cycloalkane moiety in each case. Single crystal X-ray diffractometry of **2a** confirmed the symmetrical structure for **2a** and, by extension, for **3a**. Molecular structure of **2a** is shown in Figure 3. Fractional atomic coordinates are given in Table 1 and selected bond distances and angles in Table 2.



When 3-methyl-5-phenylisoxazol-4-yl lithium (1b) was used instead of 3,5-dimethyl derivative (1a), yields of reactions with the same ketones were much lower. In each case an unique product was recovered after separation by column chromatography in the usual manner. Diastereoselectivity of reaction remained unchanged, but ^1H - and ^{13}C -nmr spectra of products (2b) and (3b) showed important differences related to stereochemistry of them. Product (2b) showed an unique signal at δ 0.87 (doublet) in ^1H -nmr and δ 12.67 in ^{13}C -nmr corresponding to methyl groups bonded to cyclopentane moiety, and a single signal at δ 43.74 in ^{13}C -nmr corresponding to C-H groups, being both spectra closely related to the corresponding spectra of 2a. Based on these data, a symmetrical meso structure was assigned to 2b, as is shown in Scheme 2.



Compound (3b) showed remarkable differences between both methyl groups bonded to the cyclohexane moiety. A signal ascribed to an equatorial methyl group was seen to δ 1.02 in ^1H -nmr as a doublet coupled ($J=7.43$ Hz) with an axial proton ($\delta=2.20$) of cyclohexane (C15 position in Figure 4). In addition a broad signal to δ 0.75 is ascribed to a shielded axial methyl group, coupled with the ortho-protons of the phenyl group at a distance of eight bonds. When the same spectrum was recorded at 100°C , the signal corresponding to the axial methyl group was seen as a doublet signal at δ 0.62 ($J=6.50$ Hz) only coupled with an equatorial proton of cyclohexane (C11 position in Figure 4). The corresponding signal of the equatorial proton was found at δ 1.93. The regions of alkyl groups in ^1H -nmr spectra of 3b at room temperature and 100°C are shown in Figures 1 and 2. Double resonance experiments confirmed the relative coupling of each methyl and C-H groups in the

cyclohexane moiety. These experiments allowed to conclude that the structure (3b) is an example of "gear effect"⁶ caused by the correlated rotation⁷ of the axial methyl group of cyclohexane and the phenyl group.

The restricted rotation observed to room temperature disappeared when ¹H- and ¹³C-nmr experiments were conducted to 100°C in deuterated DMSO. At this temperature both methyl groups in the cyclohexane moiety showed neat doublet signals in ¹H-nmr.

Single crystal X-ray diffractometry confirmed the observed structure for 3b. Crystal structure of 3b is shown in Figure 4 and crystallographic parameters are given in Tables 4 and 5. Reaction products for 1b and obtained yields are shown in Scheme 2. In this second case, yields were lower than in the first case. This fact can be due to the enhanced sterical requirements of the reaction. In all the reported reactions no by-products were obtained, and the unreacted starting materials were recovered as the corresponding 3,5-dimethyl-

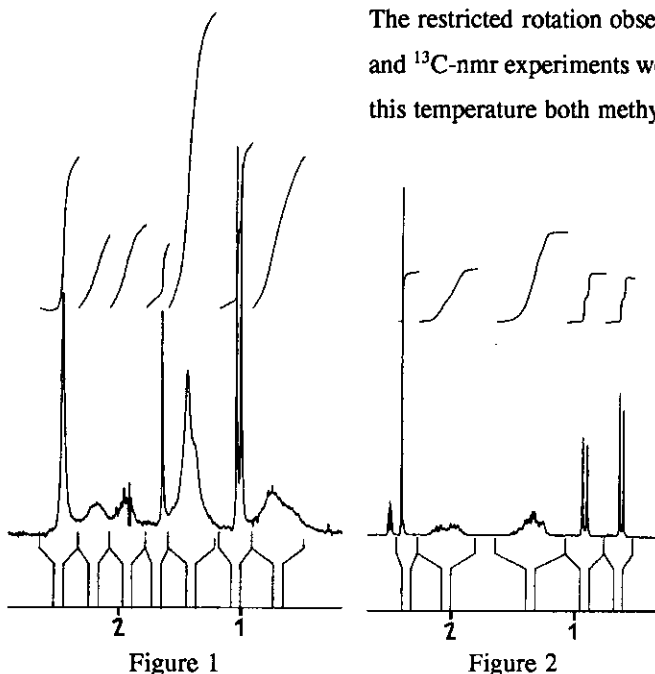


Figure 1

Figure 2

or 3-methyl-5-phenylisoxazoles arising from the hydrolysis of 1a or 1b when the reactions were worked up. The reported reactions allow to obtain single diastereoisomeric very hindered isoxazolic derivatives on one pure meso form in the cases of compounds (2a-b) and (3a), and as a racemic mixture in the case of compound (3b), starting from stereoisomeric mixtures of the corresponding α,α' -dimethylcycloalkanones by using a simple procedure.

X-Ray Crystal Structure of Compounds (2)a and (3b):⁸

Data collection and structural analysis of compound (2a). $C_{12}H_{19}NO_2$, monoclinic, space group $P2_1/c$, $a=7.763(1)$, $b=12.757(1)$, $c=12.789(1)$ Å, $\beta=91.40^\circ(1)$, $V=1266.1$ Å³, $Z=4$, $D_c=1.09$ g.cm⁻³, $\mu=5.60$ cm⁻¹. Data were collected with a four circle automatic diffractometer with graphite monochromated $CuK\alpha$ ($\lambda=1.5418$ Å) radiation and $\omega:\theta$ scan mode. From 1993 unique reflections 1848 with $I > 3\sigma(I)$ were considered as observed, corrected for Lorentz and polarization factors and used for structure solution, which was solved by direct method. Most of the hydrogen atoms were located on an difference Fourier map and the remainder placed on calculated positions. Refinement by full-matrix least squares with anisotropic thermal parameter for all non-H atoms and the hydrogen atoms as fixed isotropic contribution converged to a standard crystallographic residual of $R=0.087$. Figure 3 shows a PLUTO generated view of the molecule.

Discussion of the structure of compound (2a). The cyclopentane ring is in the envelope conformation with the C4 atom in the apical position. Both C11 and C12 methyl group are *cis* to the OH group on C4. The dihedral angle between the 1.s. plane defined by the C5, C6, C7 and C8 carbon atoms of the cyclopentane ring and the

planar isoxazole moiety is close to 90°; this arrangement leaves the C9 methyl group at the same side of the ring that the C11, C12 and OH groups. All the above together with the values of selected torsion angles and interatomic distances (showed in Table 3) indicated that the molecule has a plane of symmetry through the C7-C6 bond and the C2 carbon atom, with the OH group and the isoxazole moiety lying on this plane with the hydrogen bonded to O2 placed under the cyclopentane ring. This geometry leaves the hydroxy group rather shielded; as a consequence the crystal packing is governed by van der Waals forces and hydrogen bonds are not present.

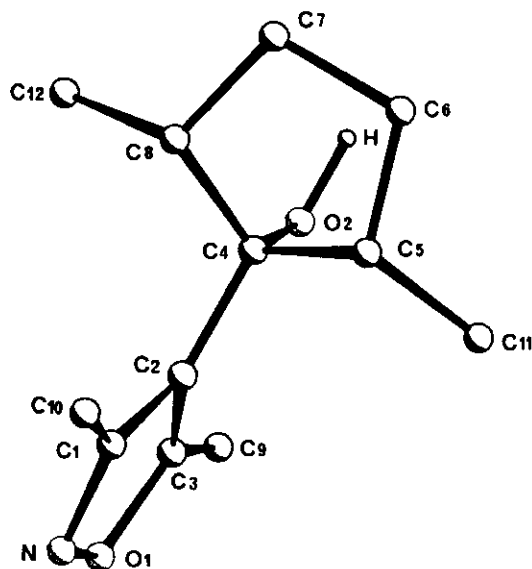


Figure 3

Table 1. Final atomic coordinates ($\times 10^4$) for **2a** with estimated standard deviations in parentheses and equivalent isotropic thermal parameters ($\text{\AA}^2 \times 10^3$).

Atom	X/A	Y/B	Z/C	U_{eq}^*
O1	1527(4)	3552(2)	4863(2)	49(1)
O2	-468(5)	2563(3)	2069(3)	71(1)
N	2655(6)	2721(3)	5119(3)	57(1)
C1	2527(6)	2069(4)	4334(4)	50(2)
C2	1357(5)	2417(3)	3543(3)	38(1)
C3	783(6)	3352(3)	3920(3)	39(1)
C4	837(5)	1911(4)	2525(3)	41(1)
C5	2320(7)	1784(4)	1759(4)	59(2)
C6	1558(8)	1049(5)	926(5)	75(2)
C7	236(9)	364(5)	1499(5)	77(2)
C8	241(8)	773(4)	2607(4)	68(2)
C9	-438(7)	4175(4)	3557(4)	63(2)
C10	3605(9)	1088(5)	4405(5)	92(3)
C11	2994(11)	2826(6)	1329(6)	103(3)
C12	-1474(11)	638(8)	3159(7)	144(5)

$$*U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Table 2. Selected bond distances ($\text{\AA}$) and angles ($^\circ$) for **2a** with estimated standard deviations in parentheses.

O1 - N	1.408(5)	C2 - C4	1.499(6)	C1 - C2 - C4	129.8(4)
O1 - C3	1.348(5)	C4 - C5	1.538(7)	C3 - C2 - C4	126.8(4)
O2 - C4	1.425(6)	C4 - C8	1.528(7)	C2 - C4 - C8	115.1(4)
N - C1	1.306(6)	C5 - C6	1.528(8)	C2 - C4 - C5	114.1(4)
C1 - C2	1.414(6)	C6 - C7	1.546(9)	O2 - C4 - C8	111.7(4)
C2 - C3	1.366(6)	C7 - C8	1.511(8)	O2 - C4 - C5	109.6(4)

Table 3. Selected torsion angles ($^\circ$) and interatomic non-bonded distances ($\text{\AA}$) of **2a**.

C1 - C2 - C4 - O2	176.0(4)	O2 --- C5	2.423 (6)
C3 - C2 - C4 - O2*	175.7(6)	O2 --- C8	2.444 (7)
C1 - C2 - C4 - C5*	116.9(6)	O2 --- C6	2.907 (7)
C3 - C2 - C4 - C5	116.6(5)	O2 --- C7	2.954 (7)
C1 - C2 - C4 - C8	51.9(6)	O2 --- C11	2.954 (7)
C3 - C2 - C4 - C8*	51.7(5)	O2 --- C12	2.939(10)

* The supplementary angle has been used.

Data collection and structural analysis of compound (3b). $C_{18}H_{23}NO_2$, triclinic, space group $P\bar{1}$, $a=9.063(1)$, $b=9.851(1)$, $c=10.093(1)$ Å, $V=789.7$ Å³, $Z=2$, $D_c=1.20$ g.cm⁻³, $\mu=5.60$ cm⁻¹. Data collected and structure solved as above, with 2187 observed reflections [$I > 3\sigma(I)$] from 2290 unique. All hydrogen atoms were located on a difference Fourier map. Refinement by full-matrix least squares with anisotropic thermal parameters for all non-H atoms and the hydrogen atoms added as fixed isotropic contribution converged to a residual of $R=0.052$. Figure 4 shows a PLUTO generated view of the molecule.

Discussion of the structure of compound (3b). The cyclohexane ring is in the chair conformation with the axial hydroxyl group on C10 oriented *trans* to the axial C16 methyl and *cis* to the equatorial C17 methyl. The dihedral angle [$136.2(1)^\circ$] between the planar isoxazole moiety and the l.s. plane defined by the C11, C12, C14 and C15 carbon atoms of the cyclohexane ring indicated a non-symmetric orientation of both rings; this fact was confirmed by the no equivalence between the torsion angles C1-C2-C10-C11 [$108.4(4)^\circ$] and C1-C2-C10-C15 [$161.1(3)^\circ$]. This arrangement leaves the OH group more accessible than in the above discussed molecule and thus can participate in the building of the crystal packing through intermolecular hydrogen bonds of the type $O_2-H\cdots N$ through the symmetry operation: $-X, -Y+1, -Z+1$, with distance $2.247(3)$ Å and angle $142.2(1)^\circ$.

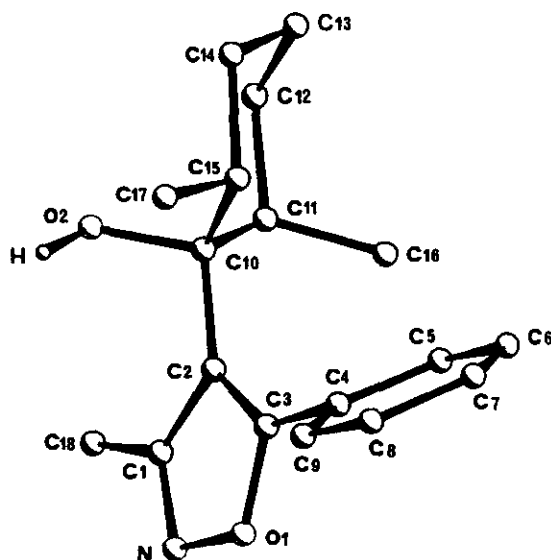


Figure 4

Table 4. Final atomic coordinates ($\times 10^4$) for 3b with estimated standard deviations in parentheses and equivalent isotropic thermal parameters ($\text{\AA}^2 \times 10^3$).

Atom	X/A	Y/B	Z/C	U_{eq}^*
O1	789(2)	7790(2)	4314(2)	389(9)
O2	-1029(3)	5195(2)	7621(2)	431(9)
N	-618(3)	6417(3)	3789(3)	398(11)
C1	-1245(3)	5994(3)	4821(3)	345(12)
C2	-284(3)	7015(3)	6075(3)	303(11)
C3	942(3)	8125(3)	5675(3)	319(12)
C4	2391(3)	9566(3)	6301(3)	333(12)
C5	2175(4)	10769(3)	6811(3)	414(14)
C6	3569(4)	12125(3)	7330(4)	486(15)
C7	5156(4)	12285(4)	7336(3)	487(14)
C8	5369(4)	11096(4)	6819(3)	489(15)
C9	3993(4)	9741(3)	6303(3)	422(14)
C10	-626(4)	6760(3)	7468(3)	335(12)
C11	-2255(4)	6924(3)	7466(3)	414(13)
C12	-2635(5)	6644(4)	8859(4)	556(17)
C13	-1163(5)	7673(4)	10062(4)	612(19)
C14	428(5)	7494(4)	10080(3)	557(17)
C15	886(4)	7334(3)	8710(3)	397(13)
C16	-2232(5)	8431(4)	7059(4)	561(17)
C17	2448(4)	7430(4)	8844(4)	547(16)
C18	-2821(4)	4571(3)	4545(3)	486(14)

$$*U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Table 5. Selected bond distances (Å) and angles (°) for **3b** with estimated standard deviations in parentheses.

O1 -N	1.409(3)	N -O1 -C3	108.5(2)	C2 -C10 -C15	113.6(2)
O1 -C3	1.368(4)	O1 -N -C1	105.5(2)	C2 -C10 -C11	110.6(2)
O2 -C10	1.454(3)	N -C1 -C2	112.7(3)	O2 -C10 -C15	108.7(2)
N -C1	1.308(4)	C1 -C2 -C10	124.6(5)	O2 -C10 -C11	103.9(2)
C1 -C2	1.438(3)	C1 -C2 -C3	103.1(2)		
C2 -C3	1.364(4)	C3 -C2 -C10	132.3(2)		
C2 -C10	1.519(4)	O1 -C3 -C2	110.2(2)		
C3 -C4	1.480(3)	C2 -C3 -C4	138.1(3)		
C10 -C11	1.548(5)	O1 -C3 -C4	111.8(2)		
C10 -C15	1.546(3)	O2 -C10 -C2	107.2(2)		

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ir spectra were registered with a Shimadzu IR-408 spectrophotometer in nujol mulls. The ^1H - and ^{13}C -nmr spectra were recorded on a Bruker AC200-E spectrometer; chemical shifts are reported in ppm from tetramethylsilane as internal standard, coupling constants in Hz. Mass spectral data were taken with a Hewlett-Packard 5970A capillary glc/mass spectrometer at 75 eV.

General Procedure for the Synthesis of **1a**, **1b**, **2a**, **3a**, **2b** and **3b**:

A vigorously stirred solution of 3,5-dimethylisoxazol-4-yl lithium⁹ (**1a**) or 3-methyl-5-phenylisoxazol-4-yl lithium (**1b**) in ether (225 ml) prepared at -55°C from 4-iodo-3,5-dimethylisoxazole (15 g, 0.067 mol) or 4-iodo-3-methyl-5-phenylisoxazole (19.1 g, 0.067 mol) and an hexane solution of *n*-butyllithium (1.6 M, 42 ml, 0.067 mol) was treated dropwise with the appropriate cyclic ketone (0.054 mol) dissolved in tetrahydrofuran (36 ml). The mixture was stirred at -55°C for 3 h and then temperature was left to reach the room temperature within a period of 5 h. The mixture was then hydrolyzed with water (250 ml), extracted with ether (5x100 ml) and the combined ethereal portions were dried with magnesium sulfate and evaporated. Separations of products were obtained by using column chromatography (120 cm length, 5 cm diameter) filled with silica gel type 60 (Merck) and benzene as eluent.

1S^{*}, **2R**^{*}, **5S**^{*}-2,5-Dimethyl-1-(3',5'-dimethylisoxazol-4'-yl)cyclopentan-1-ol (**2a**):

mp $67-68^\circ\text{C}$ (benzene-hexane); ir (Cl_4C): $\nu = 3450\text{ cm}^{-1}$ (OH), 1615 (isox); ^1H -nmr (CDCl_3): $\delta = 2.45(\text{s}, 3\text{H}, 5'-\text{CH}_3 \text{ isox}), 2.20(\text{s}, 3\text{H}, 3'-\text{CH}_3 \text{ isox}), 1.85(\text{m}, 2\text{H}, 2\times\text{CH}), 1.75(\text{s}, 1\text{H}, \text{OH}), 1.50(\text{m}, 4\text{H}, 2\times\text{CH}_2), 0.90(\text{d}, J=7.0\text{ Hz}, 6\text{H}, 2\times\text{CH}_3)$; ^{13}C -nmr (CDCl_3): $\delta = 12.47(3'-\text{CH}_3), 12.64(2-\text{CH}_3, 5-\text{CH}_3), 13.27(5'-\text{CH}_3), 29.03(3-\text{CH}_2, 4-\text{CH}_2), 43.51(2-\text{CH}, 5-\text{CH}), 81.30(\text{COH}), 115.28(4'-\text{C isox}), 157.68(3'-\text{C isox}), 166.47(5'-\text{C isox})$; ms: m/z (%) = 209 (10) [M^+], 194 (8) [M^+-CH_3], 166 (48) [$\text{M}^+-\text{CH}_3\text{CO}$], 153 (28) [$\text{M}^+-\text{CH}_2\text{CNO}$], 152 (14) [$\text{M}^+-\text{CH}_3\text{CNO}$], 124 (91) [$\text{C}_6\text{H}_6\text{NO}_2^+$], 82 (35) [$\text{C}_4\text{H}_4\text{NO}^+$], 43 (100) [CH_3CO^+], 42 (26) [CH_3CNH^+], 41 (38) [CH_3CN^+]; Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.68; H, 9.23; N, 6.52.

1S*,2R*,6S*-2,6-Dimethyl-1-(3',5'-dimethylisoxazol-4'-yl)cyclohexan-1-ol (3a):

mp 92-93 °C (benzene-hexane); ir (Nujol): $\nu = 3400 \text{ cm}^{-1}$ (OH), 1610 (isox); $^1\text{H-nmr}$ (CDCl_3): $\delta = 2.45(\text{s}, 3\text{H}, 5'-\text{CH}_3)$, $2.25(\text{s}, 3\text{H}, 3'-\text{CH}_3)$, $1.95(\text{s}, \text{exch}, 1\text{H}, \text{OH})$, $1.75(\text{m}, 2\text{H}, 2\text{xCH})$, $1.50(\text{m}, 6\text{H}, 3\text{xCH}_2)$, $0.65(\text{d}, J=6.8 \text{ Hz}, 6\text{H}, 2\text{xCH}_3)$; $^{13}\text{C-nmr}$ (CDCl_3): $\delta = 12.48(3'-\text{CH}_3 \text{ isox})$, $13.23(5'-\text{CH}_3 \text{ isox})$, $15.46(2-\text{CH}_3, 6-\text{CH}_3)$, $25.35(4-\text{CH}_2)$, $29.11(3-\text{CH}_2, 5-\text{CH}_2)$, $39.41(2-\text{CH}, 6-\text{CH})$, $75.50(\text{COH})$, $116.90(4'-\text{C isox})$, $156.07(3'-\text{C isox})$, $167.41(5'-\text{C isox})$; ms: m/z (%) = 224 (40) [$\text{M}^+ + \text{H}$], 223 (18) [M^+], 166 (51) [$\text{M}^+ - \text{CH}_3\text{CNO}$], 124 (40) [$\text{C}_6\text{H}_6\text{NO}_2^+$], 82 (22) [$\text{C}_4\text{H}_4\text{NO}^+$], 43 (100) [CH_3CO^+], 42 (24) [CH_3CNH^+], 41 (54) [CH_3CN^+]; Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.79; H, 9.47; N, 6.33.

1S*,2R*,5S*-2,5-Dimethyl-1-(3'-methyl-5'-phenylisoxazol-4'-yl)cyclopentan-1-ol (2b):

mp 103-104 °C (benzene-hexane); ir (Nujol): $\nu = 3500 \text{ cm}^{-1}$ (OH), 1615 (isox), 1585, 770, 725, 700 (phenyl); $^1\text{H-nmr}$ (CDCl_3): $\delta = 7.42(\text{m}, 5\text{H}, \text{aromatic H})$, $2.40(\text{s}, 3\text{H}, 3'-\text{CH}_3 \text{ isox})$, $2.16(\text{m}, 2\text{H}, 2\text{xCH})$, $1.76(\text{m}, 2\text{H}, 2\text{xCH})$, $1.42(\text{s}, \text{exch}, 1\text{H}, \text{OH})$, $1.38(\text{m}, 2\text{H}, 2\text{xCH})$, $0.87(\text{d}, J=7.0 \text{ Hz}, 6\text{H}, 2\text{xCH}_3)$; $^{13}\text{C-nmr}$ (CDCl_3): $\delta = 12.67(2-\text{CH}_3, 5-\text{CH}_3)$, $12.95(3'-\text{CH}_3 \text{ isox})$, $29.08(3-\text{CH}_2, 4-\text{CH}_2)$, $43.74(2-\text{CH}, 5-\text{CH})$, $81.29(\text{COH})$, $117.33(4'-\text{C isox})$, $127.95, 129.42, 129.60, 129.95(\text{C}_6\text{H}_5 \text{ aromatic C})$, $158.66(3'-\text{C isox})$, $166.78(5'-\text{C isox})$; Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.50; H, 7.75; N, 5.22.

2R*,6R*- and 2S*,6S*-2,6-Dimethyl-1-(3'-methyl-5'-phenylisoxazol-4'-yl)-cyclohexan-1-ol (3b):

mp 148-149 °C (benzene-hexane); ir (Nujol): $\nu = 3500 \text{ cm}^{-1}$ (OH), 1615 (isox), 1580, 725, 705 (phenyl); $^1\text{H-nmr}$ (CDCl_3) at room temperature: $\delta = 7.51(\text{m}, 2\text{H}, \text{ortho-aromatic H})$, $7.45(\text{m}, 3\text{H}, \text{aromatic H})$, $2.45(\text{s}, 3\text{H}, 3'-\text{CH}_3)$, $2.20(\text{m}, 1\text{H}, 2-\text{CH}_{\text{axial}})$, $1.93(\text{m}, 1\text{H}, 6-\text{CH}_{\text{equatorial}})$, $1.64(\text{s}, \text{exch}, 1\text{H}, \text{OH})$, $1.44(\text{m}, 6\text{H}, 3\text{xCH}_2)$, $1.02(\text{d}, J=7.43 \text{ Hz}, 3\text{H}, 2-\text{CH}_3 \text{ equatorial})$, $0.75(\text{m}, 3\text{H}, 5-\text{CH}_3 \text{ axial})$; $^1\text{H-nmr}$ (DMSO-d_6) at 100 °C: $\delta = 7.48(\text{m}, 5\text{H}, \text{aromatic H})$, $2.40(\text{s}, 3\text{H}, 3'-\text{CH}_3)$, $2.10(\text{m}, 1\text{H}, 2-\text{CH}_{\text{axial}})$, $1.95(\text{m}, 1\text{H}, 6-\text{CH}_{\text{equatorial}})$, $1.33(\text{m}, 6\text{H}, 3\text{xCH}_2)$, $0.92(\text{d}, J=7.62 \text{ Hz}, 3\text{H}, 2-\text{CH}_3 \text{ equatorial})$, $0.62(\text{d}, J=6.50 \text{ Hz}, 3\text{H}, 6-\text{CH}_3 \text{ axial})$; $^{13}\text{C-nmr}$ (CDCl_3) at room temperature: $\delta = 13.49(3-\text{CH}_3)$, $16.47(2-\text{CH}_3 \text{ equatorial})$, $15.80(6-\text{CH}_3 \text{ axial})$, $19.52(4-\text{CH}_2)$, $27.65(5-\text{CH}_2)$, $29.42(3-\text{CH}_2)$, $31.81(\text{br}, 2-\text{CH}, 6-\text{CH})$, $76.14(\text{COH})$, $121.36(4'-\text{C isox})$, $128.10, 129.69, 129.73, 130.48(\text{C}_6\text{H}_5 \text{ aromatic C})$, $158.35(3'-\text{C isox})$, $167.52(5'-\text{C isox})$; $^{13}\text{C-nmr}$ (DMSO-d_6) at 100 °C: $\delta = 13.59(3'-\text{CH}_3)$, $16.88(6-\text{CH}_3 \text{ axial})$, $17.36(2-\text{CH}_3 \text{ equatorial})$, $19.71(4-\text{CH}_2)$, $27.56(5-\text{CH}_2)$, $30.13(3-\text{CH}_2)$, $31.80(\text{br}, 2-\text{CH}, 6-\text{CH})$, $74.50(\text{COH})$, $120.17(4'-\text{C isox})$, $127.21, 128.69, 128.92, 130.19(\text{C}_6\text{H}_5 \text{ aromatic C})$, $157.46(3'-\text{C isox})$, $166.72(5'-\text{C isox})$; Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_2$: C, 75.75; H, 8.12; N, 4.91; Found: C, 75.88; H, 8.20; N, 4.85.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. M. Avalos, Organic Chemistry Department, University of Extremadura, Badajoz, Spain, for carrying out nmr spectra. Financial support from *Servicio de Investigación Agraria* of the *Consejería de Agricultura, Industria y Comercio de la Junta de Extremadura*, Badajoz, Spain, (Project No. 9001) is gratefully acknowledged.

REFERENCES AND NOTE

1. P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, and D. Simoni, *Synthesis*, 1987, 857.
2. T. Nishiwaki, *Synthesis*, 1975, 20.
3. A. P. Kozikowski, *Acc. Chem. Res.*, 1984, 17, 410.
4. B. E. Marron, L. Schlicksupp, and N. R. Natale, *J. Heterocycl. Chem.*, 1988, 25, 1067.
5. C. Polo, V. Ramos, T. Torroba, R. Bossio, S. Marcaccini, and R. Pepino, *Heterocycles*, 1990, 31, 811.
6. U. Berg, T. Liljefors, C. Roussel, and J. Sandström, *Acc. Chem. Res.*, 1985, 18, 80.
7. K. Mislow, *Acc. Chem. Res.*, 1976, 9, 26.
8. Crystallographic data will be deposited at the Cambridge Crystallographic Data Center.
9. C. Polo, V. Ramos, T. Torroba, and T. Antequera, *An. Quim. C.*, 1988, 84, 329.

Received, 27th May, 1991