SYNTHESIS OF 2-AZOLYLCYCLOALKANOLS

Akira Murabayashi* and Yasuo Makisumi[1]

Aburahi Laboratories, Shionogi Research Laboratories, Koka-cho, Shiga 520-34, and [1] Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Abstract — New 2-azolylcycloalkanol derivatives (**13-38**) were synthesized stereoselectively by Grignard reaction of 2-azolylcyclohexanones (**7, 8**), and particularly 2-azolylcycloheptanones (**9, 10**) afforded one of the diastereomers of 2-azolylcycloalkanols stereospecifically because the reagent attacked the carbonyl group from the less hindered side of the magnesium complex intermediate. These azolylcycloalkanols (**13-38**) were tested for antifungal activities.

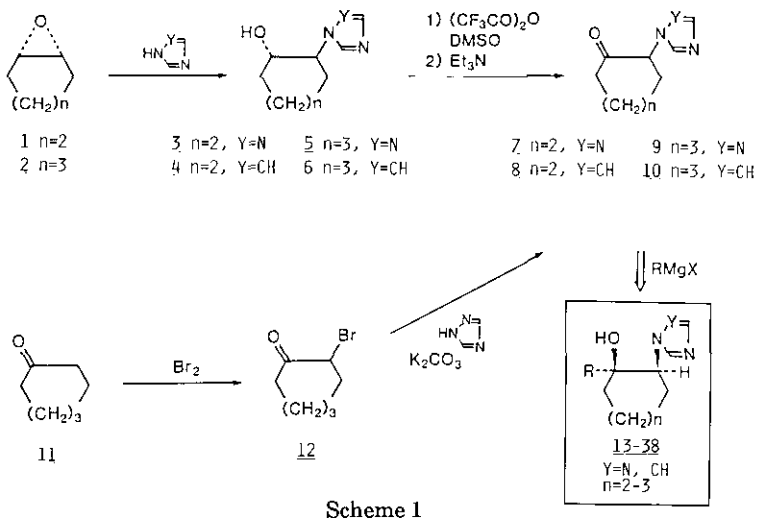
Several new antifungal agents having imidazole and triazole structures have been developed in last few years. They are effective topically in the treatment of vaginal candidasis and dermatophytosis; one of them, ketoconazole is effective orally.[1]

Active research is underway on the synthesis of orally active and broad spectrum antimycotic azole compounds. Recently,[2] 1-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-2-(1,2,4-triazol-1-yl)ethanol (ICI 153066) and 1-(4-chlorophenoxy)-2-(*t*-butyl)-3-(1,2,4-triazol-1-yl)-2-propanol (Bay n-7133) were reported to show oral antifungal activity.[3,4] They have in common a free rotatable (1,2,4-triazol-1-yl)ethanol structure. This directed us to the synthesis of azolylcycloalkanols having a rigid azolylethanol segment and the study of their antifungal activities. In this paper,[5] we report the synthesis of 2-azolylcycloalkanol derivatives *via* the stereoselective Grignard reaction of 2-azolylcycloalkanones (**7-10**).

Synthesis

The synthetic route to the target compounds (**13-38**) is shown in Scheme I. The reaction of cycloalkene oxides (**1, 2**) with azoles in ethanol or propanol yielded 2-azolylcycloalkanols (**3-6**),which were oxidized by Swern oxidation[6] to afford the 2-azolylcycloalkanones (**7-10**). 2-(1H-1,2,4-Triazol-1-yl)cycloheptanone (**10**) was also obtained from the reaction of 2-bromocycloheptanone (**12**) with 1,2,4-triazole in the presence of potassium carbonate.

Grignard reaction of 2-azolylcyclohexanones (**7-8**) with various Grignard reagents in tetrahydrofuran



Scheme 1

(THF)-ether (Et_2O) or THF gave mostly one of the diastereomers. The diastereomer ratio of ca. 95:5 was determind by high performance liquid chromatography (hplc) (Table I). The configuration of the azolyl group in these major products was assigned as equatorial from the coupling constant (J = 12, 4 Hz) of the methine proton adjacent to the N^1 in ^{1}H-nmr spectra. Because an axial orientation of the smaller hydroxyl group would be preferred, the configuration would be supposed to be cis. X-Ray crystallographic analysis of **20** supported this proposed structure (Figure 1). In the preparation of the Grignard reagents of 2-bromochlorobenzene and 1-bromo-2,5-dichlorobenzene, equimolar amounts of ethyl bromide and magnesium were used according to the procedure of Heaney *et al.*[7] to avoid the formation of benzyne.

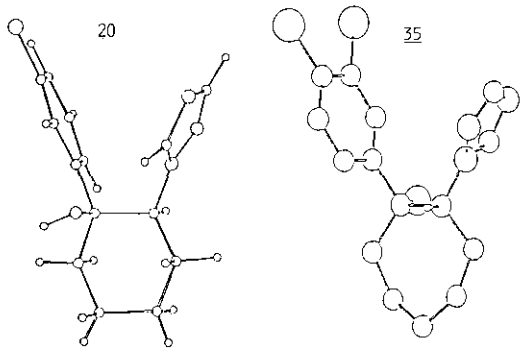
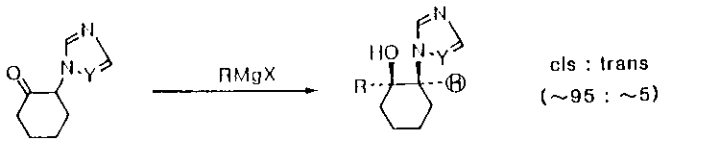
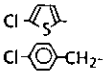


Figure 1. X-Ray crystallographic structures of **20** and **35**.

Table I. *cis*[a]-2-Azolylcyclohexanol Derivatives



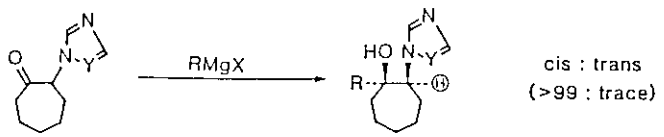
Comp. No.	R	Y	mp (°C)[b]	δ (Hz)[c] in $CDCl_3$	Yield (%)[d]
13		N	126-127	4.52 d, d (J = 12, 4)	92
14		CH	171-173	3.96 d, d (J = 12, 4)	40
15		N	112-113	4.40 d, d (J = 12, 4)	89
16		CH	183-184	3.92 d, d (J = 12, 4)	79
17		N	147-148	4.52 d, d (J = 12, 4)	71
18		N	158-160	4.52 d, d (J = 12, 4)	76
19		CH	198-199	3.98 d, d (J = 12, 4)	46
20		N	154-157	4.60 d, d (J = 12, 4)	85
21		N	142-143	5.70 d, d (J = 12, 4)	18[e]
22		N	221-222	5.45 d, d (J = 12, 4)	18[f]
23		N	146-147	--	44
24		N	131-132	4.40 d, d (J = 12, 4)	76
25		CH	82-84	3.92 d, d (J = 12, 4)	85
26		N	152-153	4.40 d, d (J = 12, 4)	61
27		N	49-51	4.17 d, d (J = 12, 4)	43
28		N	163-165	4.28 d, d (J = 12, 4)	24
29		N	129-130	4.30 d, d (J = 12, 4)	30
30	Et	N	62-63	4.20 d, d (J = 12, 4)	52

[a] The term "*cis* and *trans*" refers to the relationship of the hydroxyl and azolyl groups.
[b] All compounds were recrystallized from ether-hexane.
[c] The methine proton adjacent to the N^1.
[d] The yield of a mixture of diastereomers is shown.
[e] As a by product, **30** was obtained in 25% yield.
[f] As a by product, **30** was obtained in 17% yield.

Grignard reactions of 2-azolylcycloheptanones (**9**, **10**) gave exclusively *cis*-2-azolylcycloheptanol derivatives (**31-38**) without detectable amounts of the stereoisomers on thin layer chromatography (tlc) and hplc (Table II).

The *cis*-stereochemistry of these compounds was assumed in corroboration with X-ray crystallographic analysis of **35** (Figure 1). As for the mechanism of the observed stereoselective Grignard reaction, it is

Table II. *cis*[a]-2-Azolylcycloheptanol Derivatives



Comp. No.	R	Y	mp (°C)[b]	δ (Hz)[c] in $CDCl_3$	Yield (%)[d]
31		N	129-131	4.47 d, d (J = 11, -1)	54
32		CH	163-164	4.00 d, d (J = 11, 2)	46
33		N	152-153	4.50 d, d (J = 11, -1)	48
34		CH	164-165	3.98 d, d (J = 11, 2)	58
35		N	178-179	4.50 d, d (J = 11, -1)	34
36		N	135-136[e]	4.45 d, d (J = 11, -1)	56
37		N	170-173[e]	4.38 d, d (J = 11, -1)	61
38		N	111-112	4.23 d, d (J = 11, -1)	75

a, c, d See footnote in Table I.
b All compounds were recrystallized from ether-hexane, except **36** and **37**.
e Recrystallized from acetone-hexane.

thought that the magnesium (Mg) of the Grignard reagent forms a rigid stable complex[8] with the carbonyl oxygen and nitrogen on the azole ring of the α-keto azole (**7-10**), then R attacks the carbonyl group from the less hindered side of the intermediate as illustrated in Figure 2.

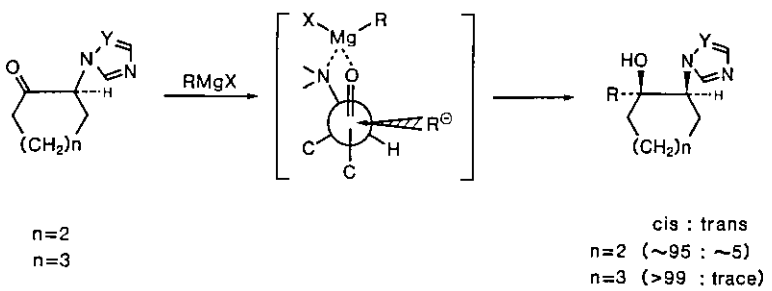
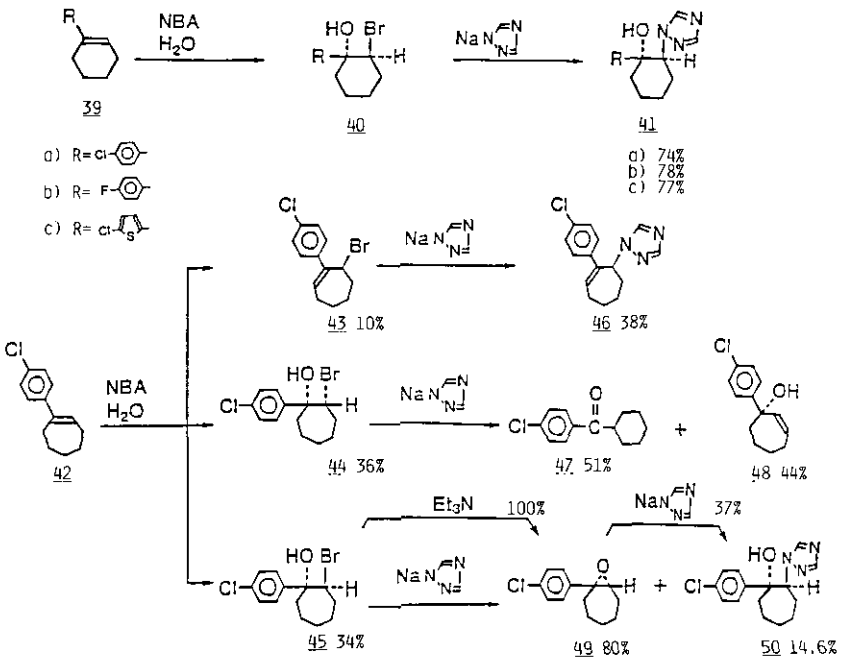


Figure 2

On the other hand, *trans*-2-(1H-1,2,4-triazol-1-yl)cyclohexanol derivatives (**41a-c**) were synthesized smoothly from sodium salt of 1,2,4-triazole and the bromohydrins (**40a-c**) which were obtained by the reaction of cyclohexene derivatives (**39a-c**) with *N*-bromoacetamide (NBA) in aqueous acetone by the method of Gravestock[9] (Scheme 2).

The reaction of 1-(4-chlorophenyl)cyclohept-1-ene (**42**) with NBA in aqueous acetone at room temperature for 6 h gave unstable oily allylic bromide (**43**, 10%) and a diastereomeric mixture of bromohydrins (**44**, **45**)



Scheme 2

which was separated by column chromatography to give crystalline **44** (36%) and oily **45** (34%). The allyl bromide (**43**) afforded 2-(4-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-cyclohept-1-ene (**46**) on heating with a sodium salt of 1,2,4-triazole in *N,N*-dimethylacetamide (DMA). Treatment of the less polar bromohydrin (**44**) with sodium salt of 1,2,4-triazole in *N,N*-dimethylformamide (DMF) gave a ring-contracted 4-chlorophenyl cyclohexyl ketone[10] (**47**, 51%) and a dehydrobrominated alcohol (**48**, 44%). The more polar isomer (**45**) was converted quantitatively to 1-(4-chlorophenyl)-1,2-epoxycyclohept-1-ene (**49**) with triethylamine (Et_3N) in dichloromethane (CH_2Cl_2). Therefore, the less polar bromohydrin (**44**) was assigned the *cis*-configuration and the more polar bromohydrin (**45**) the *trans*-one.

When the *trans*-bromohydrin (**45**) was treated with 2.2 mol of 1,2,4-triazole in the presence of NaH in DMA at 100°C for 30 h, epoxide (**49**, 80%) and *trans*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**50**, 14.6%) were obtained without any detectable amount of the *cis*-isomer on tlc. Reaction of the epoxide (**49**) with a sodium salt of 1,2,4-triazole in DMA at 100°C for 40 h gave the cycloheptanol derivative (**50**, 37.7%) and the starting material (**49**).

The formation of **43** and the diastereomeric mixture of bromohydrin (**44**, **45**) in the bromohydroxylation of 1-(4-chlorophenyl)cyclohept-1-ene (**42**) may be due to the unstability of the bromonium ion intermediate[11] of the phenylcycloheptane ring as compared with those in the phenylcyclohexane ring owing to steric interaction of 1,3-hydrogens in the (4-chlorophenyl)cycloheptane ring. Accordingly, the bromonium ion

intermediate in the phenylcycloheptane may shift to the thermodynamically more stable α-phenylcarbonium ion. The above consideration is also supported by the results that addition of halogen to *cis*- or *trans*-β-methylstyrene gave a mixture of diastereomeric dibromides *via* α-phenylcarbonium ion intermediate.[12,13]

Antifungal Activity

All the 2-azolylcycloalkanols (**13-38**, **41a-c**, **50**) were tested *in vitro* on the basis of their MIC values against three species of fungi. In general, the compounds were very active against *Tricophyton asteroides*, but slightly active or inactive against both *Candida albicans* and *Aspergillus fumigatus*. A large number of them had excellent spectra and high potency against agricultural fungi *in vivo*.

We selected (dl)-*cis*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**31**) as a candidate for further evaluation as an agricultural systemic fungicide (SSF-109).[14] Details of its antifungal activity will be described in a separate paper.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were measured with Varian T-60 and EM-90 spectrometer with tetramethylsilane as an internal standard. Ir spectra were recorded with a Hitachi 215 spectrophotometer. Hplc were analyzed with Shimadzu SPD-6A, Nucleosil $_{10}C_{18}$ 4 mm x 30 cm, at 254 nm (MeCN-MeOH-H_2O 2:1:2). Column chromatography was done on Merck Kiesel gel 60 (70-230 mesh).

2-Azolylcycloalkanols (**3-6**) — A typical example of the experimental procedure used to obtain **3-6** is as follows. A mixture of cyclohexene oxide (**1**, 9.81 g), ethanol (25 ml) and imidazole (13.6 g) was refluxed with stirring for 70 h. The ethanol was evaporated, and after addition of a small amount of water (H_2O), the residue was extracted with chloroform ($CHCl_3$). The extract was washed with a small amount of H_2O, dried over anhydrous sodium sulfate (Na_2SO_4) and evaporated to give 2-imidazolylcyclohexanol (**4**, 12.7 g, 76%) mp 134-135°C (ether-hexane). Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.10; H, 8.37; N, 16.70.

Compounds **3**, **5** and **6** were prepared by similar reaction of **1**, **2** with the corresponding azoles. **3**: 55%. mp 132-133°C (ether-hexane). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.31; H, 7.81; N, 25.00. **5**: 45%. mp 85-86°C (ether-hexane). Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.77; H, 8.32; N, 23.19. **6**: 35%, oil. Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.48; H, 9.01; N, 15.43.

2-Azolylcycloalkanone (**7-10**) — A typical example of the experimental procedure used to obtain **7-10** is as follows.

Method A). A solution of trifluoroacetic anhydride ($(CF_3CO)_2O$) (1.65 ml) in dichloromethane (CH_2Cl_2) (4 ml) was added dropwise at -78°C to a solution of dimethyl sulfoxide (DMSO) (1.05 g) in CH_2Cl_2 (10 ml). The mixture was stirred for 1 h under cooling. A solution of **5** (1.63 g) in CH_2Cl_2 (18 ml) was added dropwise and the mixture was reacted at room temperature for 2 h. Triethylamine (Et_3N) (3.75 ml) was added to the reactant at -65°C, and the temperature was raised to 0°C for 1 h. The reaction mixture was made alkaline with 5% potassium hydroxide (KOH) solution and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with $CHCl_3$-methanol (CH_3OH) (100:1) gave 2-(1H-1,2,4-triazol-1-yl)cycloheptanone (**9**, 1.16 g, 72%) mp 81-82°C (ether-hexane). Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.25; H, 7.32; N, 23.50. Ir ($CHCl_3$): 1720 (C=O) cm^{-1}. Compounds **7**, **8**, **10** were obtained in a similar way. **7**: 76%. mp 61-62°C (ether-hexane). Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.31; H, 6.60; N, 25.29. Ir ($CHCl_3$): 1731 (C=O) cm^{-1}. **8**: 25%. mp 104-105°C (ether-hexane). Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.91; H, 7.36; N, 17.01. Ir ($CHCl_3$): 1730 (C=O) cm^{-1}. **10**: 20%, mp 68-69°C (ether-hexane). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.28; H, 7.81; N, 15.70. Ir ($CHCl_3$): 1720 (C=O) cm^{-1}.

Method B). Bromine (691 g) was added dropwise to a solution of cycloheptanone (**11**, 500 g) in acetic acid (AcOH) (500 ml) and H_2O (700 ml) at 50-65°C during 40 min. After cooling, potassium carbonate (K_2CO_3) (1 kg) was added in small portions, and the reactant was poured into H_2O. The mixture was extracted with $CHCl_3$ and the organic layer was washed with H_2O, dried over Na_2SO_4 then evaporated *in vacuo* to give a crude residue **12** (867 g). A mixture of crude **12** (867 g), K_2CO_3 (924 g), 1,2,4-triazole (339 g) and acetone (2000 ml) was stirred at 70°C for 7 h. The mixture was filtrated and the filtrate was evaporated *in vacuo*. The residue was extracted with $CHCl_3$, and the organic layer was washed with brine, dried over Na_2SO_4, then evaporated *in vacuo*.

The residue was treated with ether (Et_2O) to give **9** (417.5 g, 54%).

General Procedure of the Grignard Reaction — A typical example of the experimental procedure used to synthesize 2-azolylcyclohexanol derivatives (**13-30**) and 2-azolylcycloheptanol derivatives (**31-38**) is as follows.

a) A solution of 2-(1H-1,2,4-triazol-1-yl)cyclohexanone (**7**, 1.00 g) in THF (15 ml) was added to a Grignard reagent prepared from metallic magnesium (Mg) (221 mg) and p-bromochlorobenzene (1.739 g) in anhydrous THF (12 ml) at room temperature with stirring. The mixture was stirred for 2 h, then the solution was concentrated *in vacuo*. The residue was poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel (30 g). Elution with $CHCl_3$-MeOH (100:1), gave a diastereomeric mixture of 1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cyclohexanol (**13**, 1.556 g, 92%).

[Hplc: retention time, 6.17 min (*trans*), 7.1 min (*cis*) (ratio, 4:96)]. The mixture was recrystallized from Et_2O-hexane to give *cis*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cyclohexanol (**13**) as colorless prisms. Elution with $CHCl_3$-MeOH (20:1) gave the starting material (**7**, 0.086 g).

b) A solution of 2-(1H-1,2,4-triazol-1-yl)cycloheptanone (**9**, 4.1 g) in THF (35 ml) was added to a Grignard reagent prepared from Mg (835 mg) and p-bromochlorobenzene (6.57 g) in THF (20 ml) at room temperature with stirring. The mixture was stirred at room temperature for 1 h. The reaction mixture was worked up and the residue was subjected to column chromatography on silica gel (70 g). Elution with Et_2O gave a *cis*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**31**, 3.60 g, 54%) without a detectable amount of *trans*-isomer on tlc and hplc [retention time, 9.26 min (*cis*)]. Elution with $CHCl_3$-MeOH (50:1) gave the starting material (**9**, 1.845 g). Compounds **14-30, 32-38** were prepared in a similar manner using the corresponding Grignard reagents. Their analytical data are listed in Table III.

Table III. Analytical Data for the 2-Azolylcycloalkanols (**13-38**)

Comp. No.	Formula	Analysis (%) Calcd (Found) C	H	N	Comp. No.	Formula	Analysis (%) Calcd (Found) C	H	N
13	$C_{14}H_{16}N_3OCl$	60.54 (60.59	5.80 5.87	15.13 14.87)	**26**	$C_{12}H_{14}N_3OClS$	50.79 (50.47	4.97 4.97	14.81 14.56)
14	$C_{15}H_{17}N_2OCl$	65.10 (65.10	6.19 6.22	10.12 9.98)	**27**	$C_{15}H_{18}N_3OCl$	61.75 (61.68	6.22 6.21	14.40 14.13)
15	$C_{14}H_{16}N_3OF$	64.35 (64.28	6.17 6.19	16.08 15.81)	**28**	$C_{15}H_{18}N_3OCl$	61.75 (61.92	6.22 6.44	14.40 14.28)
16	$C_{15}H_{17}N_2OF$	69.21 (69.12	6.58 6.42	10.76 10.60)	**29**	$C_{15}H_{17}N_3OCl_2$	55.23 (55.11	5.25 5.22	12.88 12.76)
17	$C_{14}H_{17}N_3O$	69.11 (69.28	7.04 7.16	17.27 17.21)	**30**	$C_{10}H_{17}N_3O$	61.51 (61.65	8.78 8.49	21.52 21.36)
18	$C_{14}H_{15}N_3OCl_2$	53.86 (53.52	4.84 4.64	13.46 13.23)	**31**	$C_{15}H_{18}N_3OCl$	61.75 (61.51	6.22 6.05	14.40 14.36)
19	$C_{15}H_{16}N_2OCl_2$	57.89 (58.03	5.18 5.21	9.00 8.92)	**32**	$C_{16}H_{19}N_2OCl$	66.09 (66.07	6.59 6.61	9.63 9.60)
20	$C_{14}H_{16}N_3OCl$	60.54 (60.55	5.81 5.51	15.13 14.86)	**33**	$C_{15}H_{18}N_3OF$	65.44 (65.36	6.59 6.54	15.26 15.06)
21	$C_{14}H_{16}N_3OCl$	60.54 (60.32	5.81 5.70	15.13 15.21)	**34**	$C_{16}H_{19}N_2OF$	70.05 (69.85	6.98 7.11	10.21 10.15)
22	$C_{14}H_{15}N_3OCl_2$	53.86 (53.71	4.84 4.71	13.46 13.42)	**35**	$C_{15}H_{17}N_3OCl_2$	55.23 (55.28	5.25 5.11	12.88 12.71)
23	$C_{18}H_{19}N_3O$	73.70 (73.66	6.53 6.44	14.32 14.21)	**36**	$C_{13}H_{17}N_3OS$	59.29 (59.50	6.51 6.60	15.96 15.86)
24	$C_{12}H_{15}N_3OS$	57.81 (57.87	6.06 6.11	16.85 16.66)	**37**	$C_{13}H_{16}N_3OClS$	52.43 (52.31	5.42 5.38	14.11 14.03)
25	$C_{13}H_{16}N_2OS$	62.87 (62.53	6.49 6.58	11.28 11.01)	**38**	$C_{16}H_{20}N_3OCl$	62.84 (62.74	6.59 6.46	13.74 13.54)

2-Bromo-1-(4-chlorophenyl)cyclohexanol (40a) — NBA (2.76 g) was added to a solution of **39a** (1.927 g) in acetone (80 ml) and water (20 ml). The reaction mixture was stirred at room temperature for 4 h and concentrated. The residue was mixed with water and extracted with benzene and the organic layer was

washed with 1% sodium thiosulfate solution, water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (30 g) with benzene. The eluate was concentrated to give **40a** (2.68 g, 92.5%) as an oily residue.

trans-1-(4-Chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cyclohexanol (41a) — 1,2,4-Triazole, sodium derivative (Aldrich) (1.87 g) was added to a solution of **40a** (2.68 g) in DMA (17 ml) and the mixture was heated at 100°C for 16 h. The reaction mixture was mixed with water and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (35 g) with Et_2O-$CHCl_3$ (1:1) to give **41a** (1.9 g, 74%) mp 187-187.5°C (benzene-hexane). Anal. Calcd for $C_{14}H_{16}N_3OCl$: C, 60.54; H, 5.80; N, 15.13; Cl, 12.76. Found: C, 60.13; H, 5.72; N, 15.02; Cl, 12.83. ^{1}H-Nmr (90 MHz) ($CDCl_3$) δ: 1.6-2.8 (8H, m), 3.4 (OH, s), 4.4 (1H, t, J = 5 Hz), 7.1 (4H, s), 7.5 (1H, s), 7.8 (1H, s). Compounds **41b,c** were obtained from **39b,c** in a similar method. **41b**: 78% mp 200-201°C (benzene-hexane). Anal. Calcd for $C_{14}H_{16}N_3OF$: C, 64.35; H, 6.17; N, 16.08; F, 7.27. Found: C, 64.11; H, 6.06; N, 16.05; F, 7.25. ^{1}H-Nmr (90 MHz) ($CDCl_3$) δ: 1.6-2.8 (8H, m), 3.0 (OH, s), 4.4 (1H, t, J = 5 Hz), 6.7-7.2 (4H, m), 7.5 (1H, s), 7.8 (1H, s). **41c**: 77% mp 170-172°C (acetone). Anal. Calcd for $C_{12}H_{14}N_3OClS$: C, 50.79; H, 4.97; N, 14.81; Cl, 12.49; S, 11.30. Found: C, 50.53; H, 4.97; N, 14.73; Cl, 12.63; S, 11.50. ^{1}H-Nmr (90 MHz) ($CDCl_3$) δ: 1.6-2.5 (m, 8H), 4.4 (1H, dd, J = 9, 5 Hz), 5.1 (OH, s), 6.5 (1H, d, J = 4 Hz), 6.6 (1H, d, J = 4 Hz), 7.9 (2H, s).

1-(4-Chlorophenyl)cyclohept-1-ene (42) — A solution of cycloheptanone (11, 16.83 g) in THF (15 ml) was added dropwise to a Grignard reagent prepared from Mg (4.35 g) and p-bromochlorobenzene (31.6 g) in THF (80 ml) under cooling during 30 min. The mixture was stirred at 60°C for 1 h. The mixture was concentrated *in vacuo*. The residue was diluted with 5% hydrochloric acid and extracted with benzene. The benzene solution was washed with 5% sodium bicarbonate ($NaHCO_3$) solution and H_2O, dried over Na_2SO_4, then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (300 g) eluting with benzene to give an oily substance (27.6 g, 82%). A solution of the above oil (24.8 g) and p-toluenesulfonic acid (1.0 g) in toluene (400 ml) was distilled by azeotropic distillation for 1 h. The toluene solution was washed with aq. K_2CO_3 and H_2O, then dried over Na_2SO_4. The solution was evaporated to give **42** (22.0 g, 96%) as a crystalline residue, mp 32-33 °C (MeOH). Anal. Calcd for $C_{13}H_{15}Cl$: C, 75.53; H, 7.3; Cl, 17.15 Found: C, 75.69; H, 7.24; Cl, 17.04.

Reaction of 1-(4-Chlorophenyl)cycloheptene (42) with NBA and H_2O — A mixture of **42** (21.99 g), NBA (17.48 g), H_2O (20 ml) and acetone (180 ml) was stirred at room temperature for 6 h. The solvent was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with benzene. The organic layer was washed with aq. $Na_2S_2O_3$, aq. Na_2CO_3 and H_2O, the solution was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel (450 g). Elution with hexane-benzene (1:1) gave a crude oil (4.83 g) containing **43** (used for next step without further purification), and

elution with benzene gave *cis*-bromohydrin (**44**, 11.623 g, 44%), mp 63-64°C (hexane). Anal. Calcd for $C_{13}H_{16}OBrCl$: C, 51.43; H, 5.31 Br, 26.32. Found: C, 51.27; H, 5.29; Br, 26.06. Ir (Nujol): 3520 cm^{-1}. ^1H-Nmr (90 MHz) ($CDCl_3$) δ: 1.5-2.5 (10H, m), 2.7 (1H, s, OH), 4.6 (1H, dd, J = 9, 4 Hz), 7.3 (4H, s, aromatic). The second fraction eluted with benzene gave *trans*-bromohydrin (**45**, 11.02 g, 34%) as an oil. Anal. Found: C, 51.50; H, 5.41; Br, 25.74. Ir (film): 3400-3500 (broad) cm^{-1}. ^1H-Nmr (90 MHz) ($CDCl_3$) δ: 1.5-2.5 (10H, m), 2.4 (1H, s, OH), 4.4 (1H, dd, J = 8, 3 Hz), 7.3 (2H, d, J = 8 Hz), 7.5 (2H, d, J = 8 Hz).

2-(4-Chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)cyclohept-1-ene (46) — A solution of crude **43** (137 mg) in DMA (3 ml) was added to a solution of sodium salt of 1,2,4-triazole prepared from 60% NaH (38 mg) and 1,2,4-triazole (66 mg) in DMA (2 ml) and the mixture was heated at 95°C for 16 h. The reaction mixture was poured into H_2O and extracted with ethyl acetate-benzene. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g). Elution with chloroform gave 2-(4-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)cyclohept-1-ene (**46**, 50 mg, 38%). mp 97-98°C (Et_2O-hexane). Anal. Calcd for $C_{15}H_{16}N_3Cl$: C, 65.81; H, 5.89; N, 15.35; Cl, 12.95. Found: C, 66.08; H, 5.98; N, 15.41; Cl, 12.97. ^1H-Nmr (90 MHz) ($CDCl_3$) δ: 1.4-2.8 (8H, m), 5.2 (1H, dd, J = 7, 2 Hz), 6.4 (1H, t, J = 6 Hz), 7.1 (2H, d, J = 9 Hz), 7.3 (2H, J = 9 Hz), 8.0 (1H, s), 8.1 (1H, s).

Base Treatment of *cis*-Bromohydrin (44) — The *cis*-bromohydrin (**44**, 305 mg) was added to a solution of sodium salt of 1,2,4-triazole prepared from 60% NaH (44 mg) and 1,2,4-triazole (83 mg) in DMF (4 ml). The reaction mixture was stirred at 100°C for 18 h. The mixture was poured into H_2O and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on a column of silica gel (10 g). The fraction eluted with hexane-benzene (3:1) gave 4-chlorophenyl cyclohexyl ketone (**47**, 112 mg, 51%). mp 59-60°C (Et_2O-hexane) [lit.[10] mp 61.5-62.5°C]. Anal. Calcd for $C_{13}H_{15}OCl$: C, 70.11; H, 6.79; Cl, 15.92. Found: C, 70.18; H, 6.97; Cl, 16.08. Ir (Nujol): 1675 (C=O) cm^{-1}.

The fraction eluted with benzene gave 1-(4-chlorophenyl)cyclohept-2-en-1-ol (**48**, 98 mg, 44%). mp 38-39°C (Et_2O-hexane). Anal. Calcd for $C_{13}H_{15}OCl$: C, 70.11; H, 6.79; Cl, 15.92. Found: C, 70.16; H, 6.86; Cl, 15.84. Ir (Nujol): 3250 (OH), 1642 (C=C) cm^{-1}. ^1H-Nmr (90 MHz) ($CDCl_3$) δ: 1.3-2.3 (8H, m), 2.4 (s, OH), 5.6 (1H, d, J = 12 Hz), 5.9 (1H, dd, J = 12, 6 Hz), 7.3 (2H, d, J = 9 Hz), 7.4 (2H, d, J = 9 Hz).

Base Treatment of *trans*-Bromohydrin (45) — *trans*-1-(4-Chlorophenyl)-2-bromocycloheptanol (**45**, 300 mg) was refluxed with Et_3N (0.3 ml) in CH_2Cl_2 (5 ml) for 30 min, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel (4 g) with benzene as the eluant, giving 1-(4-chlorophenyl)-1,2-epoxycyclohept-1-ene (**49**, 219 mg, ~100%). mp 35-36°C (Et_2O-hexane) Anal. Calcd for $C_{13}H_{15}OCl$: C, 70.11; H, 6.79; Cl, 15.92. Found: C, 69.94; H, 6.83; Cl, 16.16. ^1H-Nmr (90 MHz) ($CDCl_3$) δ: 1.4-1.7 (6H, m), 1.9-2.5 (4H, m), 2.9 (1H, t, J = 5 Hz), 7.3 (2H, s), 7.3 (2H, s).

trans-1-(4-Chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**50**) and 1-(4-Chlorophenyl)-1,2-epoxycyclohept-1-ene (**49**) — A solution of *trans*-bromohydrin (**45**, 399 mg) in DMA (2.5 ml) was added to a solution of sodium salt of 1,2,4-triazole prepared from 60% NaH (115 mg) and 1,2,4-triazole (217 mg) in DMA (2 ml). The mixture was heated at 100°C for 30 h. The reaction mixture was mixed with H_2O and extracted with ethyl acetate-benzene. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to a column of silica gel (9 g). The fraction eluted with hexane-benzene (2:1) gave 1-(4-chlorophenyl)-1,2-epoxycyclohept-1-ene (**49**, 233 mg, 80%). mp 35-36°C. The fraction eluted with chloroform-methanol (10:1) gave *trans*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**50**, 56 mg, 14.6%). mp 152-154°C (benzene-hexane). Anal. Calcd for $C_{15}H_{18}N_3OCl$: C, 61.75; H, 6.22; N, 14.40; Cl, 12.15. Found: C, 61.89; H, 6.19; N, 14.26; Cl, 12.28. ^{1}H-Nmr (90 MHz) ($CDCl_3$) δ: 1.5-2.3 (10H, m), 4.0 (br, OH), 4.7 (1H, dd, J = 8, 2 Hz), 7.1 (4H, s), 7.5 (1H, s), 7.6 (1H, s). Ir (Nujol): 3100-3400 (OH) cm^{-1}.

Ring Opening of the Epoxide (**49**) with 1,2,4-Triazole — The epoxide (**49**, 223 mg) was added to a solution of sodium salt of 1,2,4-triazole prepared from 60% NaH (80 mg) and 1,2,4-triazole (138 mg) in DMA (3 ml) and the mixture was stirred at 100°C for 40 h. The reaction mixture was mixed with H_2O and shaken with ethyl acetate and then benzene. The organic layers were combined and evaporated. The residue was chromatographed on a column of silica gel (9 g). The fraction eluted with benzene gave the starting material (**49**, 139 mg, 60%). The fraction eluted with chloroform-methanol (10:1) gave *trans*-1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl)cycloheptanol (**50**, 110 mg, 37%).

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