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ASYMMETRIC INDUCTION BY CHIRAL HETEROCYCLIC COMPOUNDS: HIGHLY DIASTEREOSELECTIVE REACTION OF 5-OXA-7,8a-DIAZA-PERHYDROAZULEN-8-ONES WITH ORGANOMETALLIC REAGENTS

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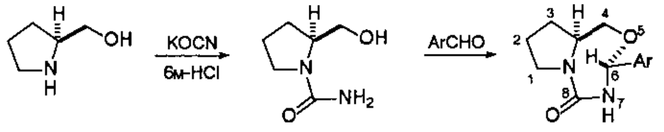
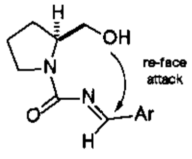
Abstract — 1) New chiral heterocyclic compounds, 5-oxa-7,8a-diazaperhydroazulen-8-ones (**3a-c**), were synthesized from (*S*)-prolinol (1) and potassium cyanate, followed by the condensation with aldehydes. 2) Extremely high diastereoselective reaction of the **3a-c** with diethylzinc proceeded with a facil procedure to give (2*S*,1′*S*)-*N*-1′-arylpropyl-2-hydroxymethyl-1-pyrrolidinecarboxamide (**4a-c**). 3) The reduction of **4a-c** with Red-Al gave (*S*)-1-aryl-*N*-methylpropylamines (**5a-c**) and (*S*)-prolinol (1) in good yields.

The diastereoselective reaction of chiral *N*-methyl-4-phenyl-1,3-oxazolidines with organometallic reagents has been reported,[1] and the 1,3-oxazolidine ring was cleaved by the attack of the reagents to the cabon atom at 2-position of the ring to give chiral amine compounds. In this work, we wish to describe a synthesis of new heterocyclic compounds, and a highly diastereoselective reaction of these



(*S*)-**1** (*S*)-**2** (3a*S*,6*R*)-**3a-c**



imine intermediate

3	Ar
a	Phenyl
b	2-Methoxyphenyl
c	1-Naphthyl

compounds.

The production of (*S*)-1-carbamoyl-2-hydroxymethylpyrrolidine (**2**) was acieved in 95% of yield by the reaction of (*S*)-prolinol (**1**) with potassium cyanate. The chiral heterocyclic compounds, 5-oxa-7,8a-diazaperhydroazulen-8-ones (**3a-c**), were synthesized in good yields by the ring closures according to the condensation of aldehydes with the amino group and the hydroxyl group of **2**.

Two diastereomeric forms could be considered by the configuration of the group at 6-position, but the products (**3a-c**) were established to consist exclusively of one isomer by analysis of ^{1}H-nmr (270 MHz) spectra. For this reason, it was considered that the ring closures proceeded by the *re*-face attack of the hydroxyl group in a preferable configuration of "the imine intermediate". The structure of **3a** was elucidated by X-ray analysis, and the absolute cofiguration was defined to be (3a*S*, 6*R*). The structures of **3a-c** were confirmed by proton nuclear magnetic resonance (^{1}H-nmr) and mass (ms) spectral analyses. The stereoscopic drawings of the structure of (3a*S*, 6*R*)-**3a** are shown in Figure 1, and the experimental results for **3a-c** are summarized in Table I.

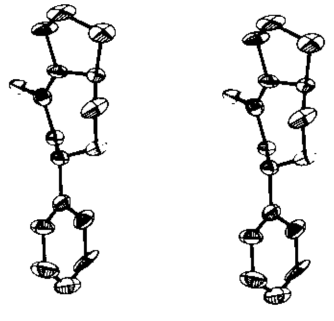


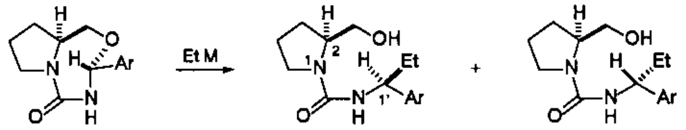
Figure 1

TABLE I 5-Oxa-7,8a-diazaperhydroazulen-8-ones (**3a-c**)

Compound	Recrystallization Solvent	Appear	Yield[a] (%)	mp (°C)	$[\alpha]_D$ (*c*)[b]	Formula	Analysis (%) Calcd (Found) C	H	N
3a	AcOEt - *n*-Hexane	Colorless columns	64	140	-75.6°(1.52)	$C_{13}H_{16}N_2O_2$	67.22 (67.00)	6.94 (6.91)	12.04 (11.85)
3b	AcOEt - *n*-Hexane	Colorless needles	61	141-142	-140.9°(1.33)	$C_{14}H_{18}N_2O_3$	64.10 (64.44)	6.92 (7.04)	10.68 (10.62)
3c	AcOEt - *n*-Hexane	Colorless needles	53	184-185	-81.9°(1.51)	$C_{17}H_{18}N_2O_2$	72.32 (72.39)	6.43 (6.45)	9.92 (9.92)

a) The yields are for isolated products. *b*) Measured in ethanol at 26-28°C, *c* is concentration.

Ethylmagnesium bromide, triethylaluminium, and diethylzinc reacted with **3a-c** giving alkylated products (**4a-c**) by the nucleophilic attack to the 6-position with the cleavage of the heterocyclic ring. *N*-1'-arylpropyl-2-hydroxymethyl-1-pyrrolidinecarboxamides (**4a-c**) were obtained in high yields, and the structures of **4a-c** were confirmed by the ^{1}H-nmr and ms spectral analyses.



(3a*S*,6*R*)-**3a-c** (2*S*,1'*S*)-**4a-c** (2*S*,1'*R*)-**4a-c**

M : MgBr , $AlEt_2$, ZnEt

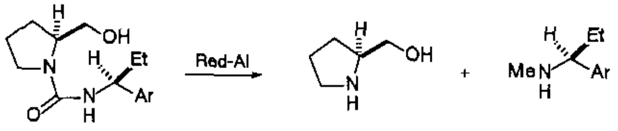
The reactions of **3a-c** with ethylmagnesium bromide and triethylaluminium afforded the diastereomeric mixtures of (2*S*,1'*S*)- and (2*S*,1'*R*)-**4a-c**, and the ratios of major and minor products were estimated by the comparison of the peak height of ^{1}H-nmr (270 MHz or 400 MHz) spectra. In the reaction with diethylzinc, the minor components of **4b** and **4c** were not observed, whereas the case of **4a** was observed a mere 7% yield of the minor compound. The products of **4a-c** were recrystallized from hexane-ether solvent to give the precipitate as colorless columns.[3] The absolute configuration of the asymmetric carbon atom of 1-arylpropylamino group was determined as described later. The experimental results are summarized in Table II.

TABLE II Diastereoselective Reaction of 5-Oxa-7,8a-diazaperhydroazulen-8-ones (3a-c) with Organometallic Reagents[a]

Reagent	Reactant	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	Product	Ratio of Isomers[c] (2*S*,1'*S*):(2*S*,1'*R*)
EtMgBr	3a	THF	0	3	89	4a	35 : 65
〃	3a	〃	-50	24	72	4a	59 : 41
〃	3b	〃	0	3	86	4b	37 : 63
〃	3b	〃	-50	24	71	4b	57 : 43
〃	3c	〃	0	3	95	4c	42 : 58
〃	3c	〃	-50	24	80	4c	61 : 39
Et_3Al	3a	CH_2Cl_2	0	3	79	4a	83 : 17
〃	3a	〃	-50	48	77	4a	92 : 8[d]
〃	3b	〃	0	3	86	4b	76 : 24
〃	3b	〃	-50	48	79	4b	77 : 23
〃	3c	〃	0	3	81	4c	88 : 12
〃	3c	〃	-50	48	78	4c	90 : 10[d]
Et_2Zn	3a	Toluene	0	3	92	4a	93 : 7
〃	3b	〃	0	3	87	4b	100 : 0
〃	3c	〃	0	3	91	4c	100 : 0

a) Reacted with 3 equimolar ammounts of reagent. *b)* Isolated yields. *c)* Estimated by ^{1}H-nmr (270MHz) spectral analysis. *d)* Used with ^{1}H-nmr (400MHz) spectrometer.

The reduction of **4a**-**c** with a sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in toluene gave (*S*)-1-aryl-*N*-methylpropylamines (**5a**-**c**) in the isolated yields of 63%, 57%, and 65%, respedtively, along with (*S*)-prolinol (**1**).



(2*S*,1'*S*)-4a-c **(*S*)-1** **(*S*)-5a-c**

The structures of **5a**-**c** were confirmed by ^{1}H-nmr and ms spectral analyses, and the specific rotations of **5a**, **5b**, and **5c** showed -36.7° (c=2.63, ethanol), -18.1° (c=3.71, ethanol), and -54.5° (c=1.73, ethanol), respectively. On the other hand, (*R*)-*N*-methyl-1-phenylpropylamine was produced from (*R*)-1-phenylpropylamine ($[\alpha]_D$ +19.7° (neat) at 23-24°C)4) by formylation with ethyl formate *in situ* by reduction with lithium aluminium hydride, and the specific rotation of this compound showed $[\alpha]_D$ +36.1° (c=2.63, ethanol). Consequently, it was determined that the absolute configuration of **5a** (major component) is *S*-form, and the configurations of **5b** and **5c** may be assiumed *S*-form in analogy with **5a**.

REFERENCES AND NOTES

1) H. Takahashi, H. Niwa, and K. Higashiyama, *Heterocycles*, 1988, 27, 2099.

2) H. Takahashi, Y. Chida, K. Higashiyama, and H. Onishi, *Chem. Pharm. Bull.*, 1985, 33, 4662.

3) (2*S*,1'*S*)-**4a**: mp 87-88°C, $[\alpha]_D$ -51.4° (c=0.30, ethanol at 28-29°C); (2*S*,1'*S*)-**4b**: mp 89-91°C, $[\alpha]_D$ -100.8° (c=0.94, ethanol at 28-29°C); (2*S*,1'*S*)-**4c**: mp 111-112°C, $[\alpha]_D$ +35.5° (c=0.68, ethanol at 28-29°C).

4) The optical purity of this compound was estimated as 92.9% from the value of $[\alpha]_D$ +21.2° (neat).5)

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