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Regio- and Stereoselective Introduction of Functional Groups into 1-Isoindolinone and 1(2*H*)-Isoquinolone Systems[1]

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The oxidation of 3*a*,4-dihydro-1-isoindolinone derivatives with MCPBA was carried out regio- and stereoselectively to afford the 5,6-epoxide products **2**. The ring opening reaction of **2** with amines, alcohols, and sodium azide gave homoallyl alcohol type of products, derived from the ring opening at C-5 of **2**. Lithium (cyano-*C*)methylcuprate reacted with **2** to give homoallyl and/or allyl alcohol, which is due to the conjugate addition to the C-7a position. This approach for selective introduction of functional groups into the heterocycles was extended for 3,4,4*a*,5-tetrahydro-1(2*H*)-isoquinolone system.

Recently, we reported the preparation of 3*a*,4-dihydro-1-isoindolinone and 3,4,4*a*,5-tetrahydro-1(2*H*)-isoquinolone derivatives, **1** and **17**, via an intramolecular "diene-regenerable" Diels–Alder reaction of 2-pyrone-6-carboxamides.[1b] Compounds **1** and **17** were regarded as cyclo-1,3-diene systems fused by lactam rings, and the lactam rings seemed to control the stereochemistry of the succeeding intermolecular Diels–Alder reaction.[1b]

A stereoselective formation of oxiranes[2] and successive ring-opening reactions[3] with various nucleophiles are recognized as a promising pathway for selective functionalization in molecules.

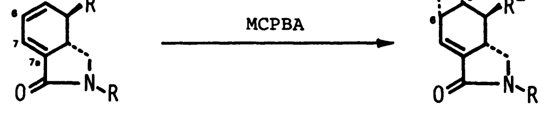
If the stereochemistry of the epoxidation of **1** and **17** is also controlled by their lactam moieties and the selective ring-opening reaction of the resulting oxiranes is possible, the selective introduction of functional groups into the above heterocyclic systems would be achieved. Thus, we investigated the epoxidation of **1** and **17** followed by ring opening reaction with several nucleophiles. The sequence of these two reactions proceeded regio- and stereoselectively and revealed to be suitable for our purpose. The regiochemistry for the ring opening reactions is also discussed.

Results and Discussion

Regio- and Stereoselective Oxidation of 3*a*,4-Dihydro-1-isoindolinones 1. The oxidation of 2-phenyl- (**1a**), 2-benzyl-4-methyl- (**1b**), and 2-benzyl-4-phenyl-3*a*,4-dihydro-1-isoindolinone (**1c**) with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane-water at room temperature resulted in epoxidation of the 5,6-double bond of **1a—c**, and the oxiranes **2a—c** were isolated in almost quantitative yields as single isomers (Scheme 1). The configuration between the oxirane and lactam rings of **2** was assigned to be syn on the basis of the values of the coupling constants among the protons and the 3a-, 4-, 5-, and 6-positions of **2a—c** (Table 1). For **2a** the vicinal coupling constants J_{3a-4} (7.5 and 11.7 Hz) between methine (3a-position) and methylene (4-position) were assignable as cis and trans[1b] and J_{4-5} (2.8 and ca. 0 Hz) to be also cis and trans,[4] respectively. The values of J_{3a-4} (ca. 10.5 Hz) and J_{4-5} (less than 1 Hz) for **2b** or **2c** are deduced to be trans and trans configurations among the three protons.

Therefore, the oxygen is introduced to the C–C double bond on the same side as the lactam ring with high stereoselectivity regardless of the kind of substituent at the 4-position. The syn-directing effect of allylic hydroxyl[5] or allylic amido group[6] is well-known in the stereoselective epoxidation of the cyclohexene system by peracids. Interestingly, the lactam ring of **1** causes an excellent syn-directing effect, nevertheless it is located far from the oxidized double bond in this case.

Ring Opening Reaction of Oxiranes 2 with Nucleophiles. The oxiranes **2a—c** have four reaction sites for nucleophiles as demonstrated in Fig. 1. In order to establish the regioselectivity of the nucleophilic attack, we examined for the first time the reaction with hard bases[7] such as heteroatomic



1 2

a: R=Ph, R^1=H; b: R=CH_2Ph, R^1=CH_3; c: R=CH_2Ph, R^1=Ph

Scheme 1.

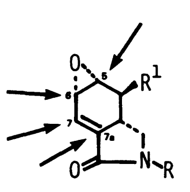


Fig. 1. Reaction sites of oxiranes **2** for nucleophiles.

nucleophiles. Recently, Posner et al. reported that the ring opening of oxiranes with nucleophiles proceeded smoothly in the presence of commercially available neutral alumina.[8]

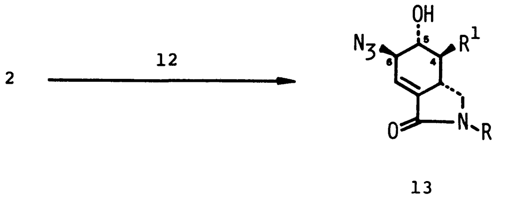
In a similar manner to Posner's method, **2a**—**c** were allowed to react with benzylamine (**3**) and pyrrolidine (**4**) to afford homoallyl alcohols, **5a**—**c** and **6a**—**c**, derived from the ring opening at the C-5 of **2**. No products derived from that of C-6 were observed. The structural assignment for the homoallyl alcohols was accomplished on the basis of their spectral data. Especially, in their mass spectra the fragment ion peaks due to the elimination of aldehydes from the molecular ion, $M^+-R^1CH_2CHO$, were observed. The stereochemical relationships between the functional groups carrying oxygen and nitrogen atoms could not be determined only from the coupling constants because of the complexity of the signal patterns. However, these were tentatively assigned to be trans according to the reaction pathway[9] reported heretofore.

The analogous reaction of **2b** with methanol (**7**) and 1-pentanol (**8**) gave the same type of adducts **9** and **10** together with diol **11**, respectively. Under similar conditions the ring opening of **2b** with water afforded **11** in only 19% yield with the recovery of **2b** (64%). Therefore, the formation of **11** in the reaction with alcohol would be attributable to the secondary reaction via **9** or **10**.

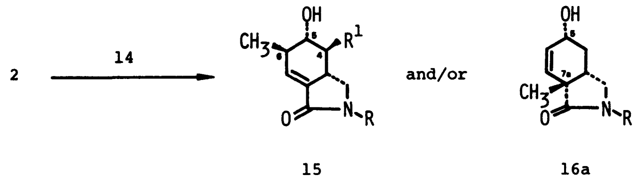
The ring opening of **2** using azide ion as a softer base was examined. The reaction of **2a**—**c** with sodium azide (**12**) in aqueous THF gave homoallyl alcohols **13a**—**c** in good yields.

These results are shown in Schemes 2 and 3. The regio- and stereochemistries of these adducts were confirmed on the basis of the similarities of the spectral data to those of the adducts with amines.

The introduction of an alkyl group into the 1-oxoisoindoline system was finally investigated. The reaction of **2** with Grignard reagents or alkyllithiums afforded only disappointing results. So, the reaction

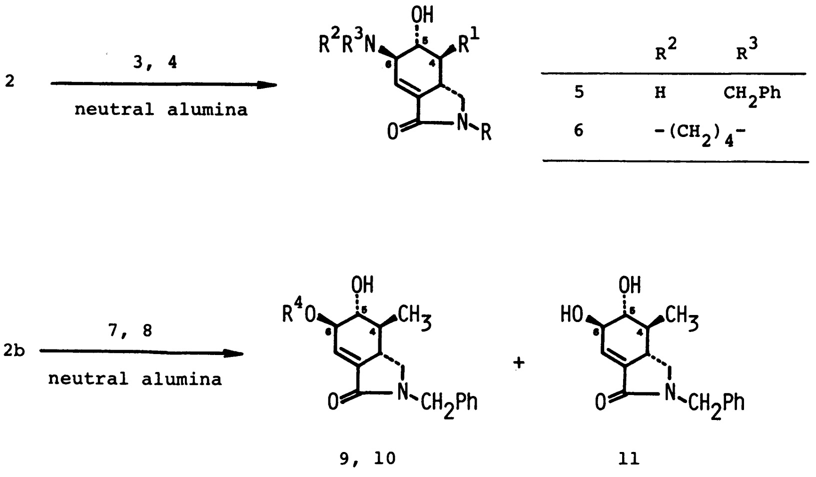


Scheme 3.



Products	(Yield/%)
15a (32)	16a (9)
15b (60)	———
15c (44)	———

Scheme 4.



	R^2	R^3
5	H	CH_2Ph
6	$-(CH_2)_4-$	

R^4	Products	(Yield/%)
CH_3	9 (68)	11 (12)
$n-C_5H_{11}$	10 (27)	11 (53)

Scheme 2.

of **2** with lithium (cyano-*C*)methylcuprate (**14**) was examined, which is widely used as an effective reagent for opening oxiranes.[10] Oxirane **2a** reacted with **14** in THF at −30 °C to give homoallyl alcohol **15a** and allyl alcohol **16a**, which was derived from the conjugate addition of methyl anion onto the C-7a. However, in a similar reaction of **2b** or **2c** with **14**, only homoallyl alcohol **15b** or **15c** was obtained (Scheme 4).

The structure of **16a** was elucidated on the basis of its spectral data. In its ^{1}H NMR spectrum, two olefinic proton signals at δ=6.44(doublet) and 5.72 (double doublet) were observed. Its mass spectrum showed a fragment ion peak due to (M^+-CH_3), but the peak characteristic of a homoallyl alcohol type of product, M^+-CH_3CHO, was not observed.

The relationship between the methyl group at the 7a-position and the hydroxyl at the 5-position is tentatively assigned to be trans because the conjugate addition of lithium alkyl(cyano-*C*)cuprates to 1,3-diene monooxides have been shown to proceed in a highly selective manner.[11] This assignment is also supported by the findings that the conjugate addition of **14** only occurs at the reaction with **2a**, which bears the least hindered substituent (R^1=H) at the 4-position among oxiranes **2**.

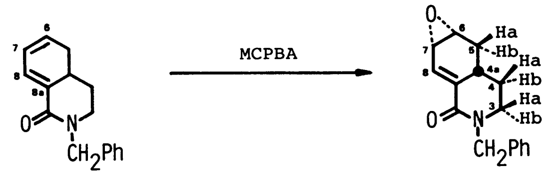
The hard and soft acid–base concept[7] appears to be useful in considering the regioselectivities of these ring-opening reactions. According to the concept, the 5- and 6-positions are hard and the 7- and 7a-position are soft reaction sites,[12] respectively. The reaction with hard nucleophiles as well as with azide ion occurred exclusively at the 6-position, which is more reactive than the 5-position owing to it being an allylic position. Methyl anion prefers to react with the softer acid site, e.g., C-7a position. However, the regiochemistry of the addition was eventually determined on the balance between the affinity and the steric hinderance, which becomes serious for attack at the 7a-position when the substituent at the 4-position is bulky.

Regio- and Stereoselective Oxirane Formation of 3,4,4*a*,5-Tetrahydro-1(2*H*)-isoquinolone System and Its Ring Opening Reaction. The regio- and stereoselective oxidation of **1** to **2** followed by the regioselective ring opening allowed to the introduction of functional groups into the 3*a*,4-dihydro-1-isoindolinone system. Accordingly, we investigated the oxidation of 2-benzyl-3,4,4*a*,5-tetrahydro-1(2*H*)-isoquinolone (**17**), a higher homolog of **1**, and the successive introduction of functional groups into the 1(2*H*)-isoquinolone system.

The oxidation of **17** with MCPBA in dichloromethane–water below 0 °C[13] and treatment by column chromatography on silica gel gave an oxirane **18**, resulting in oxidizing of the 6,7-double bond of **17**, in 84% yield (Scheme 5).

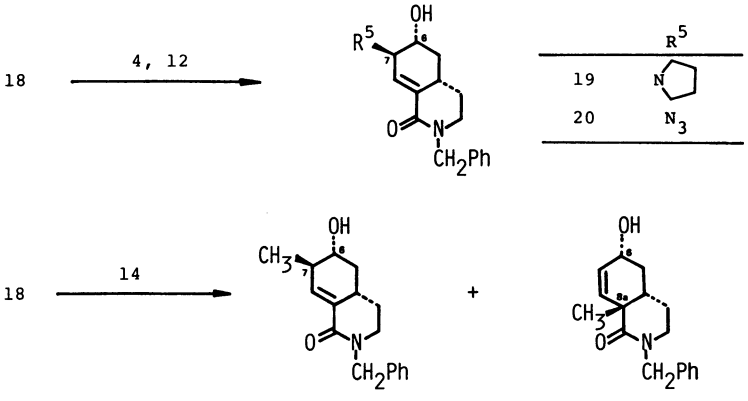
The structure of **18** was confirmed on the basis of spectral data and, especially, the configuration between the oxirane and lactam rings was also syn. Therefore, the fused lactam moiety in **17** as well as **1** caused the directing effect in the oxidation with MCPBA.

The ring opening reaction of **18** with pyrrolidine (**4**) and sodium azide (**12**) gave homoallyl alcohol type of products **19** and **20**. On one hand, oxirane **18** reacted with lithium (cyano-*C*)methylcuprate (**14**) to afford homoallyl alcohol **21** and allyl alcohol **22** in 60 and 21% yields, respectively (Scheme 6).



17 18

Scheme 5.



	R^5
19	N(pyrrolidinyl)
20	N_3

21 22

Scheme 6.

Experimental

General. All melting points are uncorrected. The IR spectra were measured on a JASCO IRA-1 spectrometer. The ^{1}H NMR spectra were obtained on JEOL FX-200, FX-100, and/or JMN-MH-100 spectrometers. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ov, overlapped with each other. The mass spectra were determined with a JEOL JMS-012G-2 or JMS-D spectrometer and at an ionization energy of 75 eV. The elemental analyses were performed on a Hitachi 026 CHN analyzer. The progress of most reactions was monitored by thin-layer chromatography (Silica gel 60F-254, Merck). The visualization was made with ultraviolet light (254 and 365 nm). Wakogel C-200 and C-300 were used for the preparative chromatography. As catalysts for the ring opening of the oxiranes, Woelm-200 neutral alumina (activity grade I) was used.

Epoxidation of 3*a*,4-Dihydro-1-isoindolinones 1 with MCPBA. Typical Procedure: A mixture of 0.50 g (2.4 mmol) of **1a** and 0.57 g (3.3 mmol) of MCPBA in dichloromethane-water (60—20 mL) was stirred for 12 h at room temperature. After destroying the excess MCPBA with sodium hydrogensulfite, the organic layer was collected and evaporated to dryness. The residue was subjected to a short column chromatography on silica gel (chloroform) to afford 0.51 g (96%) of oxirane **2a**.

2a: Colorless plates (benzene); mp 168—169 °C; IR (KBr) cm^{-1}: 1670 (CO); MS *m/z* (rel intensity) 227 (M$^+$, base peak) and 77 (77).

Found: C, 73.97; H. 5.76; N, 6.26%. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%.

2b: Yield 100%; colorless plates (benzene); mp 139—140 °C; IR (KBr) cm^{-1}: 1660 (CO); MS *m/z* (rel intensity) 255 (M$^+$, 40) and 91 ($C_7H_7^+$, base peak).

Found: C, 75.25; H, 6.66; N, 5.60%. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%.

2c: Yield 99%; colorless prisms (benzene); mp 139—140 °C; IR (KBr) cm^{-1}: 1660 (CO); MS *m/z* (rel intensity) 317 (M$^+$, 48) and 91 ($C_7H_7^+$, base peak).

Found: C, 79.44; H, 6.05; N, 4.55%. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41%.

The ^{1}H NMR spectral data for **2** are demonstrated in Table 1.

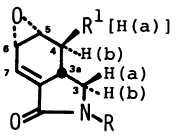
Reaction of Oxiranes 2 with Amines. Typical Procedure: A mixture of 300 mg (1.32 mmol) of **2a** and 710 mg (6.64 mmol) of benzylamine (**3**) in dry THF (10 mL) was stirred in the presence of 10 g of the neutral alumina for 6 h at room temperature. The alumina was filtered off and washed with methanol. The filtrate was collected and evaporated to dryness. The residue was subjected to column chromatography on silica gel (chloroform) to give 280 mg (63%) of **5a**.

5a: Colorless needles (ethanol); mp 186—188 °C; IR (KBr) cm^{-1}: 3320 (OH), 3280 (NH), and 1650 (CO); ^{1}H NMR (CDCl$_3$) δ=1.56 (1H, m, 4-Hb), 2.16 (1H, m, 3a-H), 2.4—3.2 (3H, ov, 4-Ha, OH, and NH), 3.24 (1H, m, 6-H), 3.45 (1H, t, 3-Hb, $J_{gem}=J_{3\text{-}3a}=9.5$ Hz), 3.84 (1H, m, 3-Ha), 3.92 (2H, s, -CH$_2$-Ph), 4.05 (1H, m, 5-H), 6.55 (1H, br s, 7-H), and 7.0—7.8 (10H, m, phenyl); MS *m/z* (rel intensity) 334 (M$^+$, 6), 290 (M$^+$—CH$_3$CHO, base peak), 199 (290—CH$_2$Ph, 46), and 77 (92).

Found: 75.61; H, 6.70; N, 8.37%. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38%.

5b: Yield 73%; colorless needles (ethanol); mp 197—199 °C; IR (KBr) cm^{-1}: 3320 (OH), 3270 (NH), and 1640 (CO); ^{1}H NMR (CDCl$_3$) δ=1.04 (3H, d, CH$_3$, J=8.5 Hz), 1.54 (1H, m, 4-H), 2.4—2.9 (3H, ov, 3a-H, NH, and OH), 2.90

Table 1. ^{1}H NMR Spectral Data for Oxiranes **2** in CDCl$_3$: δ



Compd	3-H(a)	3-H(b)	3a-H	4-H(a)	4-H(b)	5-H	6-H	7-H	Others
2a	4.03	3.5—3.6	3.03	2.73	1.47	3.65	3.5—3.6	6.89	7.1—7.7 (Phenyl)
	t	a)	m	ddd	dd	dd	a)	t	
	J (Hz): 3(a)-3(b)=3(a)-3a=9.6, 3a-4(a)=7.2, 3a-4(b)=11.7, 3a-7=4.6, 4(a)-4(b)=14.2, 4(a)-5=2.8, 4(b)-5=0, 5-6=3.4, 6-7=4.6								
2b	3.47	2.91	2.53		1.58	3.35	3.54	6.75	1.25 (CH$_3$)
	t	dd	m		dq	d	t	t	4.45, 4.62 (-CH$_2$-Ph)
	J (Hz): 3(a)-3(b)=3(a)-3a=10.2, 3(b)-3a=7.2, 3a-4=10.5, 3a-7=4.5, 4-5=0, 5-6=4.5, 6-7=4.5								7.2—7.4 (Phenyl)
2c	3.17	2.9	2.9		2.62	3.57	3.54	6.87	4.48, 4.63 (-CH$_2$-Ph)
	t	a)	a)		d	d	t	t	
	J (Hz): 3(a)-3(b)=12.0, 3a-4=10.3, 3a-7=3.9, 4-5=0, 5-6=3.9, 6-7=3.9								7.2—7.4 (Phenyl)

a) Overlapped with each other.

(1H, t, 3-Hb, $J_{gem}=J_{3-3a}=9.5$ Hz), 3.32 (1H, m, 6-H), 3.42 (1H, t, 3-Ha, $J_{gem}=J_{3-3a}=9.5$ Hz), 3.80 (1H, br, s, 5-H), 3.93 (2H, s, $-CH_2-Ph$), 4.41, 4.63 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=16.2$ Hz), 6.50 (1H, br s, 7-H), and 7.1—7.6 (10H, m, phenyl); MS *m/z* (rel intensity) 362 (M^+, 10), 304 ($M^+-CH_3CH_2CHO$, 57), 213 ($304-CH_2Ph$, 37), and 91 ($C_7H_7^+$, base peak).

Found: C, 75.96; H, 7.22; N, 7.57%. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73%.

5c: Yield 53%; colorless needles (ethanol); mp 139—141 °C; IR (KBr) cm^{-1}: 3250 (OH), 3000 (NH), and 1670 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.9$ (2H, br s, OH and NH), 2.6—2.9 (2H, ov, 3-Hb and 4-H), 3.28 (1H, t, 3-Ha, $J_{gem}=J_{3-3a}=9.5$ Hz), 3.3—3.6 (2H, ov, 3a-H and 6-H), 3.90 (3H, ov, 5-H and CH_2-Ph), 4.41 (2H, s, $-CH_2-Ph$), 6.50 (1H, br s, 7-H), and 7.0—7.4 (15H, m, phenyl); MS *m/z* (rel intensity) 424 (M^+, 8), 406 (M^+-H_2O, 4), 304 (M^+-PhCH_2CHO, 35), 213 ($304-CH_2Ph$, 21), and 91 ($C_7H_7^+$, base peak).

Found: C, 79.09; H, 6.85; N, 6.67%. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.21; H, 6.65; N, 6.60%.

6a: Yield 74%; colorless needles (ethanol); mp 182—184 °C; IR (KBr) cm^{-1}: 3050 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.62$ (1H, m, 4-Hb), 1.77 (4H, m, pyrrolidinyl), 2.15 (1H, m, 3a-H), 2.70 (4H, m, pyrrolidinyl), 3.0—3.4 (3H, ov, 4-Ha, 6-H, and OH), 3.52, 3.98 (1H each, 2t, 3-Hb and 3-Ha, $J_{gem}=J_{3-3a}=9.2$ Hz), 4.15 (1H, m, 5-H), 6.68 (1H, br s, 7-H), and 7.0—7.8 (5H, m, phenyl); MS *m/z* (rel intensity) 298 (M^+, 8), 254 (M^+-CH_3CHO, base peak), and 77 (17).

Found: C, 72.37; H, 7.56; N, 9.23%. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39%.

6b: Yield 89%; colorless needles (ethanol); mp 141—143 °C; IR (KBr) cm^{-1}: 3120 (OH) and 1670 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.05$ (3H, d, CH_3, $J=7.7$ Hz), 1.5 (1H, m, 4-H), 1.8 (4H, m, pyrrolidinyl), 2.65 (1H, m, 3a-H), 2.75 (4H, m, pyrrolidinyl), 2.95, 3.44 (1H each, 2t, 3-Hb and 3-Ha, $J_{gem}=J_{3-3a}=9.4$ Hz), 3.24 (1H, br s, 6-H), 4.00 (1H, br s, 5-H), 4.32 (1H, br s, OH), 4.35, 4.70 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=16.3$ Hz), 6.55 (1H, br s, 7-H), and 7.1—7.5 (5H, m, phenyl); MS *m/z* (rel intensity) 326 (M^+, 2), 268 ($M^+-CH_3CH_2CHO$, base peak), 177 ($268-CH_2Ph$, 62), and 91 ($C_7H_7^+$, 73).

Found: C, 73.79; H, 8.10; N, 8.74%. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58%.

6c: Yield 71%; colorless needles (ethanol); mp 212—215 °C; IR (KBr) cm^{-1}: 3050 (NH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.78$, 2.68 (4H each, 2m, pyrrolidinyl), 2.75—3.05 (3H, ov, 3-Hb, 3a-H, and 4-H), 3.15—3.7 (3H, ov, 3-Ha, 6-H, and OH), 4.12 (1H, m, 5-H), 4.39, 4.61 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=15.8$ Hz), 6.62 (1H, br s, 7-H), and 7.1—7.5 (10H, m, phenyl); MS *m/z* (rel intensity) 388 (M^+, 2), 268 (M^+-PhCH_2CHO, base peak), 177 (268-CH_2Ph, 91), and 91 ($C_7H_7^+$, 63).

Found: C, 77.35; H, 7,34; N, 7.25%. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21%.

The reaction of **2** with alcohols was performed in a similar manner to that with amines.

9: Colorless oil; IR (Neat) cm^{-1}: 3390 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.01$ (3H, d, CH_3, $J=7.4$ Hz), 1.53 (1H, m, 4-H), 2.5—3.3 (2H, ov, 3-Hb and 3a-H), 3.3—3.4 (1H, m, 3-Ha), 3.38 (3H, s, OCH_3), 3.76 (1H, br s, OH), 3.82 (1H, br s, 5-H), 4.08 (1H, m, 6-H), 4.35, 4.52 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=15.7$ Hz), 6.43 (1H, br s, 7-H), and 7.0—7.4 (5H, m, phenyl); MS *m/z* (rel intensity) 287 (M^+, 10), 229 ($M^+-CH_3CH_2CHO$, 28), 138 ($229-CH_2Ph$, 13), and 91 ($C_7H_7^+$, base peak).

Found: *m/z* 287.1528. Calcd for $C_{17}H_{21}NO_3$: M, 287.1520.

10: Colorless oil; IR (Neat) cm^{-1}: 3380 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=0.7$—1.8 (10H, m, ov, 4-H and butyl), 1.05 (3H, d, CH_3, $J=7.7$ Hz), 2.90 (1H, m, 3a-H), 2.93 (1H, t, 3-Hb, $J_{gem}=J_{3-3a}=8.6$ Hz), 3.2—3.7 (4H, ov, 3-Ha, $-CH_2-O$, and OH), 3.90 (2H, ov, 5- and 6-H), 4.45, 4.62 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=16.0$ Hz), 6.52 (1H, br s, 7-H), and 7.1—7.4 (5H, m, phenyl); MS *m/z* (rel intensity) 343 (M^+, 2), 285 ($M^+-CH_3CH_2CHO$, 12), and 91 ($C_7H_7^+$, base peak).

Found: *m/z* 343.2147. Calcd for $C_{21}H_{29}NO_3$: M, 343.2146.

11: Colorless plates (ethanol); mp 180—182 °C; IR (KBr) cm^{-1}: 3380—3320 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.06$ (3H, d, CH_3, $J=7.1$ Hz), 1.70 (1H, m, 4-H), 2.6—3.1 (2H, ov, 3a-H and OH), 2.97, 3.49 (1H each, 2t, 3-Hb and -Ha, $J_{gem}=J_{3-3a}=7.7$ Hz), 3.8 (1H, m, 5-H), 4.14 (1H, br d, OH, $J=4.9$ Hz), 4.24 (1H, m, 6-H), 4.58 (2H, s, $-CH_2-Ph$), 6.52 (1H, br s, 7-H), and 7.35 (5H, m, phenyl); MS *m/z* (rel intensity) 273 (M^+, 23), 215 ($M^+-CH_3CH_2CHO$, 23), 124 ($215-CH_2Ph$, 11), and 91 ($C_7H_7^+$, base peak).

Found: C, 70.50; H, 7.08; N, 5.20%. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13%.

Reaction of 2 with Sodium Azide (12). Typical Procedure: A mixture of 500 mg (2.20 mmol) of **2a** and 160 mg (2.46 mmol) of **12** in aqueous THF (20 mL) was stirred for 5 h at room temperature. The reaction mixture was extracted with chloroform (20 mL×3) and the organic layer was evaporated to dryness. The residue was subjected to column chromatography on silica gel with chloroform–ethyl acetate (3/1) elution to give 400 mg (67%) of **13a**.

13a: Colorless prisms (chloroform); mp 132—133 °C; IR (KBr) cm^{-1}: 3370 (OH), 2080 (N_3), and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.5$ (1H, m, 4-Hb), 2.12 (1H, m, 3a-H), 3.1—3.6 (2H, ov, 4-Ha and OH), 3.63, 4.08 (1H each, 2t, 3-Hb and -Ha, $J_{gem}=J_{3-3a}=8.3$ Hz), 4.03 (1H, br s, 5-H), 4.28 (1H, br s, 6-H), 6.65 (1H, br s, 7-H), and 7.2—7.9 (5H, m, phenyl); MS *m/z* (rel intensity) 270 (M^+, 69), 229 (31), 228 (M^+-N_3, 28), and 77 (base peak).

Found: C, 62.00; H, 5.28; N, 20.68%. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N; 20.73%.

13b: Yield 74%; colorless prisms (ethanol); mp 74—76 °C; IR (KBr) cm^{-1}: 3230 (NH), 2050 (N_3), and 1640 (CO); ^{1}H NMR ($CDCl_3$) $\delta=1.08$ (3H, d, CH_3, $J=9.0$ Hz), 1.56 (1H, br dq, 4-H, $J_{3a-4}=11.8$ and $J_{4-Me}=9.0$ Hz), 2.89 (1H, m, 3a-H), 2.96, 3.49 (1H each, 2t, 3-Hb and -Ha, $J_{gem}=J_{3-3a}=10.7$ Hz), 3.07 (1H, br s, OH), 3.89 (1H, br s, 5-H), 4.07 (1H, br s, 6-H), 4.47, 4.70 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=16.9$ Hz), 6.50 (1H, br s, 7-H), and 7.2—7.5 (5H, m, phenyl); MS *m/z* (rel intensity) 298 (M^+, 21), 256 (M^+-N_3, 98), and 91 ($C_7H_7^+$, base peak).

Found: C, 64.51; H, 6.08; N, 18.85%. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78%.

13c: Yield 65%; colorless prisms (ethanol); mp 160—162 °C; IR (KBr) cm^{-1}: 3290 (OH), 2090 (N_3), and 1660 (CO); ^{1}H NMR ($CDCl_3$) $\delta=2.70$ (1H, m, 4-H), 2.90, 3.40 (1H each, 2t, 3-Hb and -Ha, $J_{gem}=J_{3-3a}=9.2$ Hz), 3.0—3.8 (2H, ov, 3a-H and OH), 4.10 (1H, br s, 5-H), 4.24 (1H, br s, 6-H), 4.45, 4.68 (1H each, 2d, $-CH_2-Ph$, $J_{gem}=16.0$ Hz), 6.62 (1H, br s, 7-H), and 7.2—7.6 (10H, m, phenyl); MS *m/z* (rel intensity) 360 (M^+, 18), 318 (M^+-N_3, 89) and 91 ($C_7H_7^+$, base peak).

Found: C, 69.81; H, 5.66; N, 15.68%. Calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55%.

Reaction of 2 with Lithium (Cyano-*C*)methylcuprate (14). Typical Procedure: To a mixture of 580 mg (6.5 mmol) of cuprous cyanide and 10 mL of THF, 6.4 mmol of methyllithium was added under nitrogen atmosphere at −78 °C. The temperature was slowly raised to −30 °C, and 500 mg (2.2 mmol) of **2a** in THF (2 mL) was injected into the reaction mixture. The mixture was stirred at the same temperature for an additional one hour, then warmed up to 0 °C and kept at that temperature for 6 h. The mixture was made acidic with conc. hydrochloric acid and extracted with dichloromethane (20 mL×3). The organic layer was collected and evaporated to dryness. The residue was subjected to column chromatography on silica gel (chloroform–ethyl acetate: 4/1) to give 180 mg (32%) of **15a** and 50 mg (9%) of **16a**.

15a: Colorless needles (ethanol); mp 163—164 °C; IR (KBr) cm^{-1}: 3400 (OH) and 1670 (CO); ^{1}H NMR ($CDCl_3$) δ=1.05 (3H, d, CH_3, J=8.0 Hz), 1.40 (1H, ddd, 4-Hb, J_{gem}=12.6, J_{3a-4}=11.2, and J_{4-5}=2.0 Hz), 2.16 (1H, ddd, 4-Ha, J_{gem}=12.6, J_{3a-4}=5.7, and J_{4-5}=4.8 Hz), 2.45 (1H, m, 6-H), 2.67 (1H, br d, OH, J=4.0 Hz), 3.18 (1H, m, 3a-H), 3.49, 3.95 (1H each, 2t, 3-Hb, and -Ha, J_{gem}=J_{3-3a}=8.8 Hz), 3.98 (1H, m, 5-H), 6.49 (1H, t, 7-H, J_{3a-7}=J_{6-7}=2.8 Hz), and 7.1—7.5 (5H, m, phenyl); MS *m/z* (rel intensty) 243 (M^+, base peak), 200 (24), 199 (M^+-CH_3CHO, 71), and 77 (52).

Found: C, 73.88; H, 7.16; N, 5.86%. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%.

16a: Colorless oil; IR (Neat) cm^{-1}: 3380 (OH) and 1680 (CO); ^{1}H NMR ($CDCl_3$) δ=1.10 (3H, s, CH_3), 2.02 (1H, m, 4-Hb), 2.13 (1H, dd, 4-Ha, J_{gem}=15.7 and J_{3a-4}=7.0 Hz), 2.2—2.7 (2H, ov, 3a-H and OH), 3.5—3.6 (2H, ov, 3-Ha and -Hb), 4.36 (1H, br s, 5-H), 5.72 (1H, dd, 6-H, J_{5-6}=5.0 and J_{6-7}=11.7 Hz), 6.44 (1H, d, 7-H, J_{6-7}=11.7 Hz), and 7.0—7.7 (5H, m, phenyl); MS *m/z* (rel intensity) 243 (M^+, base peak), 228 (M^+-CH_3, 7), 106 (62), and 77 (44).

Found: *m/z* 243.1254. Calcd for $C_{15}H_{17}NO_2$: M, 243.1258.

15b: Colorless oil; IR (Neat) cm^{-1}: 3400 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) δ=1.06 (3H, d, CH_3, J=7.1 Hz), 1.39 (1H, m, 4-H), 2.4—3.1 (4H, ov, 3-Hb and -Ha, 3a-H, and 6-H), 3.50 (1H, br s, OH), 3.66 (1H, m, 5-H), 4.44, 4.74 (1H each, 2d, $-CH_2-Ph$, J_{gem}=15.4 Hz), 6.47 (1H, br s, 7-H), and 7.2—7.6 (5H, m, phenyl); MS *m/z* (rel intensity) 271 (M^+, 84), 214 (57), 213 ($M^+-CH_3CH_2CHO$, 25), 122 (11), and 91 ($C_7H_7^+$, base peak).

Found: *m/z* 271.1573. Calcd for $C_{17}H_{21}NO_2$: M, 271.1571.

15c: Colorless prisms (ethanol); mp 176—177 °C; IR (KBr) cm^{-1}: 3310 (OH) and 1660 (CO); ^{1}H NMR ($CDCl_3$) δ=1.19 (3H, d, CH_3, J=7.7 Hz), 2.23 (1H, m, 4-H), 2.5—2.8 (2H, ov, 6-H and 3a-H), 2.83, 3.38 (1H each, 2t, 3-Hb and -Ha, J_{gem}=J_{3-3a}=9.2 Hz), 3.58 (1H, br s, OH), 3.83 (1H, m, 5-H), 4.45, 4.67 (1H each, 2d, $-CH_2-Ph$, J_{gem}=15.7 Hz), 6.58 (1H, t, J_{3a-7}=J_{6-7}=3.0 Hz), and 7.2—7.5 (10H, m, phenyl); MS *m/z* (rel intensity) 333 (M^+, 47), 214 (73), 213 (M^+-PhCH_2CHO, 10), and 91 ($C_7H_7^+$, base peak).

Found: C, 79.45; H, 6.98; H, 4.51%. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20%.

Formation of Oxirane 18 and Its Ring Opening Reaction with Nucleophiles 4, 12, and 14. The oxidation of **17** with MCPBA was performed in a similar manner to that of **1** with the exception of reaction temperature (below 0 °C).[13]

18: Colorless oil; IR (Neat) cm^{-1}: 1600 (CO); ^{1}H NMR ($CDCl_3$) δ=1.42 (1H, m, 5-Hb), 1.55 (1H, m, 4-Hb), 1.86 (1H, m, 4-Ha), 2.40 (1H, ddd, 5-Ha, J_{gem}=14.2, J_{4-5}=8.4, and J_{5-6}=3.3 Hz), 2.55 (1H, m, 4a-H), 3.21 (1H, ddd, 3-Hb, J_{gem}=13.9, J_{3-4}=5.7, and J_{3-4}=3.2 Hz), 3.33 (1H, ddd, 3-Ha, J_{gem}=13.9. J_{3-4}=12.6, and J_{3-4}=3.7 Hz), 3.48 (1H, t, 7-H, J_{6-7}=J_{7-8}=4.5 Hz), 3.59 (1H, dd, 6-H, J_{5-6}=3.3 and J_{6-7}=4.5 Hz), 4.55, 4.76 (1H each, 2d, $-CH_2-Ph$, J_{gem}=16.2 Hz), and 7.2—7.4 (6H, ov, 8-H and phenyl); MS *m/z* (rel intensity) 255 (M^+, 45), 164 (M^+-CH_2Ph, 8), and 91 ($C_7H_7^+$, base peak).

Found: *m/z* 255.1264. Calcd for $C_{16}H_{17}NO_2$: M, 255.1258.

The ring opening reactions of **18** with **4**, **12**, and **14** were performed in similar manners to those of the corresponding reactions of oxirane **2**.

19: Colorless prisms (ethanol); mp 156—158 °C; IR (KBr) cm^{-1}: 3390 (OH) and 1610 (CO); ^{1}H NMR ($CDCl_3$) δ=1.25 (1H, m, 5-Hb), 1.5—2.1 (7H, ov, 4-Ha and -Hb, 5-Ha, and pyrrolidinyl), 2.5—2.9 (5H, ov, 4a-H and pyrrolidinyl), 3.18 (1H, m, 3-Hb), 3.2—3.6 (3H, ov, 3-Ha, 7-H, and OH), 4.02 (1H, m, 6-H), 4.76 (2H, s, $-CH_2-Ph$), 7.15 (1H, br s, 8-H), and 7.3—7.6 (5H, m, phenyl); MS *m/z* (rel intensity) 326 (M^+, 41), 282 (M^+-CH_3CHO, base peak), 191 (282—CH_2Ph, 76), and 91 ($C_7H_7^+$, 89).

Found: C, 73.49; H, 8.21; N, 8.30%. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58%.

20: Colorless prisms (ethanol); mp 117—118 °C; IR (KBr) cm^{-1}: 3400 (OH), 2100 (N_3), and 1610 (CO); ^{1}H NMR ($CDCl_3$) δ=1.2—1.8 (2H, ov, 4-Ha and 5-Hb), 1.7—2.2 (2H, ov, 4-Ha and 5-Ha), 2.76 (1H, m, 4a-H), 3.3—3.6 (2H, ov, 3-Ha and -Hb), 3.88 (3H, ov, 6-H, 7-H, and OH), 4.65, 4.89 (1H each, 2d, $-CH_2-Ph$, J_{gem}=16.0 Hz), 7.05 (1H, m, 8-H), and 7.3—7.6 (5H, m, phenyl); MS *m/z* (rel intensity) 298 (M^+, 12), 256 (M^+-N_3, 40), 91 ($C_7H_7^+$, 51), and 42 (base peak).

Found: C, 64.59; H, 6.17; N, 18.82%. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78%.

21: Colorless needles (ethanol); mp 170—171 °C; IR (KBr) cm^{-1}: 3400 (OH) and 1600 (CO); ^{1}H NMR ($CDCl_3$) δ=1.05 (3H, d, CH_3, J=8.6 Hz), 1.2—1.7 (2H, ov, 4-Hb and 5-Hb), 1.6—2.1 (2H, ov, 4-Ha and 5-Ha), 2.2—2.9 (2H, ov, 4a-H and 7-H), 3.1—3.6 (3H, ov, 3-Ha and -Hb, and OH), 3.91 (1H, br s, 6-H), 4.64, 4.89 (1H each, 2d, $-CH_2-Ph$, J_{gem}=16.0 Hz), 7.08 (1H, br s, 8-H), and 7.4 (5H, m, phenyl); MS *m/z* (rel intensity) 271 (M^+, 78), 227 (M^+-CH_3CHO, 23), 136 (227—CH_2Ph, 9), and 91 ($C_7H_7^+$, base peak).

Found: C, 75.07; H, 7.84; N, 5.27%. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16%.

22: Colorless needles (benzene-hexane); mp 143—145 °C; IR (KBr) cm^{-1}: 3310 (OH) and 1615 (CO); ^{1}H NMR ($CDCl_3$) δ=1.18 (3H, s, CH_3), 1.6—2.0 (4H, ov, 4-Ha and -Hb and 5-Ha and -Hb), 2.24 (1H, m, 4a-H), 2.76 (1H, br s, OH), 3.0—3.5 (2H, ov, 3-Ha and -Hb), 4.26 (1H, br s, 6-H), 4.41, 4.89 (1H each, 2d, $-CH_2-Ph$, J_{gem}=16.2 Hz), 5.90 (1H, dd, J_{6-7}=5.4 and J_{7-8}=11.7 Hz), 6.79 (1H, d, 8-H, J_{7-8}=11.7 Hz), and 7.4 (5H, m, phenyl); MS *m/z* (rel intensity) 271 (M^+, 76), 256 (M^+-CH_3, 17), 180 (M^+-CH_2Ph, 10), 148 (24), and 91 ($C_7H_7^+$, base peak).

Found: C, 75.20; H, 7.98; N, 5.33%. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.27%.

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References

1) a) Cycloaddition Reactions of 2-Pyrones and Related Compounds. Part V; b) For part IV of this series: M. Noguchi, S. Kakimoto, H. Kawakami, and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, **59**, 1355 (1986).

2) For recent reviews: G. Berti, "Topics in Stereochemistry," John Wiley & Sons, New York (1973), Vol. 2; K. B. Sharpless, *Aldrichimica Acta*, **12**, 63 (1979); P. A. Bartlett, *Tetrahedron*, **36**, 2 (1980).

3) For recent reviews: S. Patai, "The Chemistry of the Ether Linkage," John Wiley & Sons, New York (1967); T. J. Mason, *Heterocyclic Chem.*, **3**, 1 (1982); J. G. Smith, *Synthesis*, **1984**, 629.

4) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).

5) T. Itoh, K. Kaneda, and S. Teranishi, *J. Chem. Soc., Chem. Comm.*, **1976**, 421; T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *Tetrahedron Lett.*, **1976**, 3157; *Idem*, *J. Am. Chem. Soc.*, **101**, 159 (1979).

6) J.-E. Bäckvall, K. Oshima, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **44**, 1953 (1979).

7) T.-S. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York (1977).

8) G. H. Posner, D. Z. Rogers, C. M. Kinzing, and G. M. Gurria, *Tetrahedron Lett.*, **1975**, 3597; G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.*, **99**, 8208 (1977); G. H. Posner, S. Moon, and P. E. Peterson, *Synth. Commun.*, **11**, 737 (1981).

9) A. Rosowsky, "Heterocyclic Compounds with Three- and Four-Membered Rings," ed by A. Weissberger, Interscience Pub. Inc., New York (1964) and also (see Ref. 4).

10) R.-D. Acker, *Tetrahedron Lett.*, **1977**, 3407 and **1978**, 2399.

11) J. P. Marino and N. Hatanaka, *J. Org. Chem.*, **44**, 4467 (1979); J. P. Marino and H. Abe, *Synthesis*, **1980**, 872; *idem*, *J. Am. Chem. Soc.*, **103**, 2907 (1981).

12) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973).

13) The reaction at room temperature gave undesirable results; lowering the yield of **18** and producing side reaction products including dioxiranes.