A NEW SYNTHETIC ROUTE TO FUNCTIONALIZED 2-AZABICYCLO[2.2.2]OCTANE

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Abstract - Functionalized 2-azabicyclo[2.2.2]octane ring system was prepared *via* intramolecular S_N2 ring opening of epoxide by an amide anion.

In the course of our studies on the enantioselective synthesis of natural products utilizing 5-trimethylsilyl-2-cyclohexenone (**1**), we had a chance to examine diastereoselective 1,4-additions of various nucleophiles to **1**, and found that the 1,4-addition of nitromethane to **1** proceeds in a highly diastereoselective manner.[1] The result prompted us to examine new enantioselective routes to aza-containing bicyclic compounds from **1**. Azabicyclo[2.2.2]octane, the isoquinuclidine system, was chosen as a target molecule since the system is common to Iboga-type indole alkaloids[2] of which (+)-catharantine is of special interest because of its role as a synthetic precursor of clinical anticancer agent Vinblastine and related alkaloids.[3] The retro-synthetic route is shown in Figure 1.

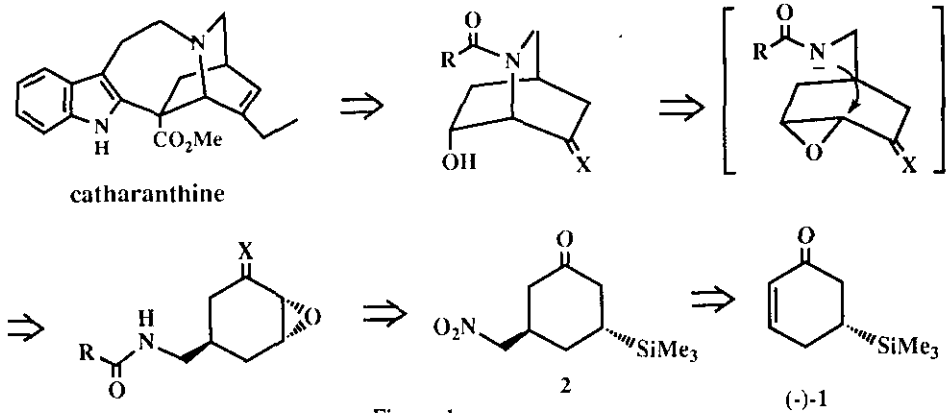
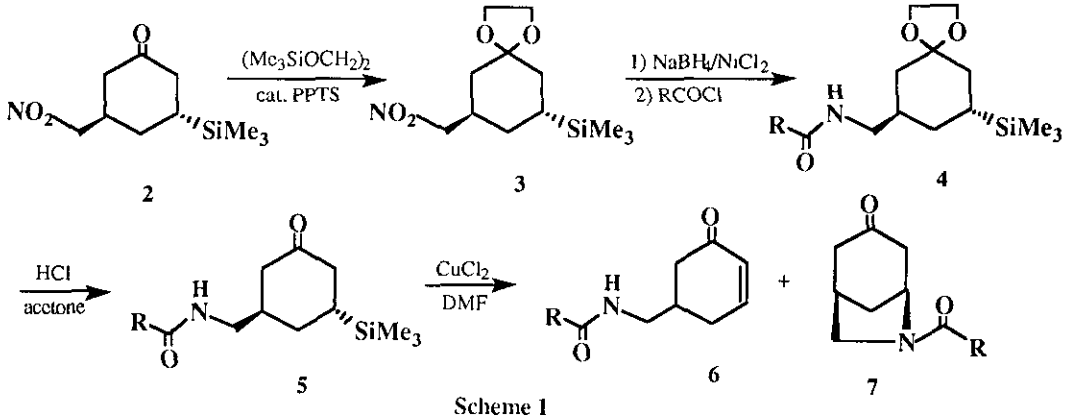


Figure 1

The KF-alumina catalyzed 1,4-addition of nitromethane to (-)-**1** afforded the adduct (+)-**2** (diastereopurity: ~95%) in 78% yield. The diastereomerical enrichment by recrystallization at this stage was unsuccessful due to its low crystallinity but it was easily carried out on the acetal derivative [(-)-**3**]. Though the optically pure compound is thus accessible, we started our work with racemic **3**. Conversion of the nitro group into amide moiety was carried out by nickelboride reduction[4] ($NaBH_4/NiCl_2$, room temperature 10 min, MeOH) followed by acylation with acyl chloride or acid anhydride to give **4** whose deprotection afforded the corresponding **5** in good overall yields (Table 1). Desilylation under halogenation conditions ($CuCl_2$, 60°C, 50 min, DMF) gave **6**. When **5** is a carbamate derivative, the cyclized compound (**7**) was formed as a major product (Scheme 1, Table 1).



2 **3** **4** **5** **6** **7**

Scheme 1

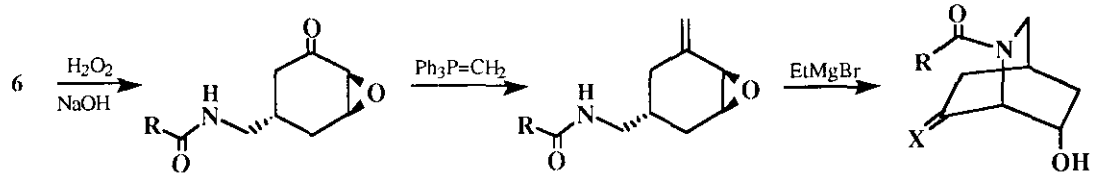
Table 1. Preparation of **5** and **6**.

Entry	R	**5**	Yield[a] (%)	Yield (%)	**6**	7
1	Ph	**5a**	85		62	-
2	$PhCH_2O$	**5b**	77		10	69
3	MeO	**5c**	80		trace	42
4	CF_3	**5d**	81		50	-
5	3-Indolylmethyl	**5e**[b]	85		57	21

a) Overall yield from **3**. b) Acylation was carried out with 3-indolacetic acid and EDC {1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride}.

Epoxidation of enone (**6a,d,e**) under basic conditions (H_2O_2, cat 6M NaOH, room temperature 10 min) gave epoxides (**8**) (95~90% d.e.). After recrystallization, the diastereomerically pure **8a** was treated with bases such as DBU, benzyltriethylammonium chloride-NaOH, t-BuOK, and LDA under various conditions, however, expected isoquinuclidine derivative (**10a**) was not isolated. Presumably the main reason for these results is ascribed to the instability of the product, β-hydroxy ketone, under the basic conditions. Therefore, the carbonyl

group was converted to the methylene group by the Wittig reaction. Reactions of **8a** and **8e** with 2-10 eq. of the Wittig reagent gave **9a** and **9e** in high yields (89 and 91%). Treatment of **9a** with 3 eq. of EtMgBr in THF at 0 °C for 0.5 h gave the expected isoquinuclidine **11a** in 88% yield. In the case of **9e**, the reaction was rather sluggish (room temperature, for 45 min) and addition of 1 eq. of HMPA was necessary. The isoquinuclidine derivatives obtained here bear functionality at 6 and 7 positions which are convenient for the conversion into catharantine or ibogamine nuclei. These results are shown in Scheme 2.



8a: R=Ph 88%
d: R=CF_3 67%
e: R=3-Indolylmethyl 88%

9a: 89%
e: 91%

10 : X=O
11 : X=CH_2
a : 88%
e : 54%

Scheme 2

Since the optically pure starting material is accessible and the subsequent conversions are of high diastereoselectivities, the above route offers a new enantioselective route[5] to functionalized isoquinuclidine ring system.

EXPERIMENTAL

^1H And ^{13}C nmr were recorded on a JEOL JNM-EX270 in $CDCl_3$. Ir was recorded on a Hitachi 260-50. The specific rotation was measured on a Horiba SEPA-200. Mass spectra were recorded on Shimazu GCMS QP-2000A mass spectrometers.

3-Nitromethyl-5-trimethylsilylcyclohexanone ethylene acetal [(±)-3 and (-)-3]. A toluene solution of **2** (29.31 g, 128 mmol), bistrimethylsiloxyethane (96 g, 466 mmol), and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) was heated at 90 °C for 3 h. After cooling to a room temperature, saturated $NaHCO_3$ solution was added and the reaction mixture was extracted with ether. Flash column chromatography (hexane:ether=5:1) of the product gave **3** (32.5 g, 93 %). (±)-**3**: mp 46.5-47.0 °C (MeOH). ^1H Nmr δ -0.03 (*s*, 9H), 0.98-1.11 (m, 1H), 1.30-1.44 (m, 2H), 1.55-1.82(m, 4H), 2 80 (m, 1H), 3.92 (s, 4H), 4.56-4.71 (m, 2H); ^{13}C nmr δ -3.7, 17.4, 27.5, 33.9, 35.7, 36.4, 64.1, 64.6, 78.3, 107.9; ir (KBr): 1560 (NO_2) cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_4Si$: C, 52.72; H, 8.55; N, 5.12. Found: C, 52.79; H, 5.25. (-)-**3**: mp 47.5-48.5 °C (MeOH). $[\alpha]_D^{23}$ -32.6°(*c 1 0*, $CHCl_3$).

3-Benzoylaminomethyl-5-trimethylsilylcyclohexanone ethylene acetal (4a). To a solution of $NiCl_2 \cdot 6H_2O$

(11.6 g, 49.1 mmol) in MeOH (800 ml) was added $NaBH_4$ (5.57 g, 147.3 mmol) in small portions. After stirring for 0.5 h, **3a** (26.80, 98.2 mmol) in MeOH (50 ml) was added to the mixture, and then additional amounts of $NaBH_4$ (13.07 g, 346 mmol) was added. After 10 min, the mixture was filtered through a short pad of celite. The celite was washed with MeOH, and the combined MeOH solution was concentrated. Addition of 1M aq. NaOH to the residue, extraction with ether, and condensation of the ether layer gave the amine derivative which was used without further purification. To a dry THF (500 ml) solution of the crude amine was added Et_3N (23 ml, 165 mmol) and the mixture was cooled to 0 °C. Benzoyl chloride (10.3 ml, 86.4 mmol) was added and the solution was stirred at 0 °C for 10 min and then at room temperature for 20 min. After removal of THF, water was added to the residue and the product was extracted with CH_2Cl_2. Condensation and recrystallization gave **4a** (25g). The mother liquor was condensed and purified by flash column chromatography (hexane:AcOEt=2:1) to give further amount (4.5 g) of **4a** (combined yield 87%). mp 147.5-148.0 °C (hexane-AcOEt). ^1H Nmr δ -0.04 (s, 9H), 1.09-1.20 (m, 1H), 1.28-1.40 (m, 2H) 1.57-1.85 (m, 4H), 2.29 (m, 1H), 3.40-3.50(m, 1H), 3.69-3.79(m, 1H), 3.89-4.00 (m, 4H), 6.45 (br s, 1H), 7.39-7.52 (m, 3H), 7.74-7.78 (m, 2H); ^{13}C nmr δ -3.6, 17.6, 27.7, 33.9, 35.4, 36.5, 42.4, 63.9, 64.6, 108.8, 126.8, 128.6, 131.2, 135.1, 167.4; ir (KBr): 3260 (NH), 1620 (C=O) cm^{-1} Anal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.67; H, 8.41; N, 4.03. Found: C, 65.63; H, 8.39; N, 3.87.

3-(3-Indolylacetyl)aminomethyl-5-trimethylsilylcyclohexanone ethylene acetal (4e). To a cooled (0 °C) solution of 3-indolacetic acid (1.48 g, 8.44 mmol) in dry CH_2Cl_2 (40 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 1.78 g, 9.29 mmol) and 1-hydroxybenzotriazole (HOBT, 1.26 g, 9.29 mmol). After 1 h, the crude amine (2.05 g, 8.44 mmol), which was prepared as mentioned in the synthesis of **4a**, and triethylamine (1.29 ml, 9.29 mmol) were added to the solution. After stirred at 0 °C for 1 h and at room temperature overnight, the reaction was quenched with saturated $NaHCO_3$ solution. Extraction and purification by flash column chromatography (hexane:AcOEt=1:2) gave **4e** (3.05 g, 90%) as a foam. ^1H Nmr δ -0.13 (s, 9H), 0.92-0.97 (m, 1H), 1.12-1.35 (m, 3H), 1.43-1.52 (m, 3H), 2.05 (m, 1H), 3.06-3.16 (m, 2H), 3.41-3.59 (m, 3H), 3.66-3.73 (m, 1H), 3.75 (s, 2H), 5.86 (br s, 1H), 7.14-7.23 (m, 3H), 7.39 (d, J=7.6 Hz, 1H), 7.58 (d, J=7.6 Hz, 1H), 8.51 (s, 1H); ^{13}C nmr δ -3.7, 17.2, 27.3, 33.4, 33.4, 35.5, 35.6, 41.4, 63.7, 64.1, 108.4, 108.5, 111 6, 118.5, 119.9, 122.3, 124.2, 126.9, 136.6, 172.0; ir (KBr): 3420, 3310 (NH), 1655(C=O) cm^{-1}. Ms (70 ev) m/z (rel intensity) 400 (M^+; 7), 355 (22), 226 (35), 213 (30), 131 (20), 130 (100).

3-Benzoylaminomethyl-5-trimethylsilylcyclohexanone (5a). To an acetone solution (600 ml) of **4a** (19.19 g, 55.3 mmol) was added 2M HCl (170 ml). After stirred for 1 h, the mixture was basified with saturated

$NaHCO_3$ solution and concentrated. Extraction followed by purification by recrystallization and column chromatography (hexane:AcOEt=4:3) gave **5a** (16.45 g, 98%). mp 91.5-92 °C (hexane-AcOEt). ^1H Nmr δ -0.01 (s, 9H), 1.31-1.43 (m, 1H), 1.68-1.78 (m, 2H), 2.12-2.34 (m, 3H), 2.49-2.59 (m, 2H), 3.13-3.23 (1H, m), 3.56-3.66 (m, 1H), 6.44 (br s, 1H), 7.38-7.52 (m, 3H), 7.73-7.76 (m, 2H); ir (KBr): 3350 (NH), 1702, 1653 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_2Si$: C, 67.28; H, 8.30; N, 4.62. Found: C, 67.13; H, 8.31: N, 4.67.

3-Benzyloxycarbonylaminomethyl-5-trimethylsilylcyclohexanone (5b). *Oil.* ^1H *Nmr δ -0.01 (s, 9H), 1.26-*1.37 (m, 1H), 1.68-1.73 (m, 2H), 2.10-2.33 (m, 3H), 2.43-2.53 (m, 2H), 2.99-3.09 (m, 1H), 3.22-3.33 (m, 1H), 4.87 (br s, 1H), 5.09 (s, 2H), 7.29-7.37 (m, 5H); ir (neat): 3350 (NH), 1720 (C=O) cm^{-1}. Ms (70 ev) m/z (rel intensity) 242 (4), 181 (21), 91 (100).

3-Methoxycarbonylaminomethyl-5-trimethylsilylcyclohexanone (5c). mp 51.5-52.0 °C (hexane-AcOEt). ^1H Nmr δ *-0.01 (s, 9H), 1.29 (m, 1H), 1.69-1.84 (m, 2H), 2.10-2.32 (m, 3H), 2.46-2.53 (m, 2H), 2.97-3.07 (m,* 1H), 3.19-3.30 (m, 1H), 3.65 (s, 3H), 4.87 (br s, 1H); ir (KBr): 3350 (NH), 1735, 1700 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_3Si$: C, 55.99; H, 9.01; N, 5.44 Found: C, 55.72; H, 9.16; N, 5.43.

3-Trifluoroacetylaminomethyl-5-trimethylsilylcyclohexanone (5d) mp 86.0-86.5 °C (hexane-AcOEt). ^1H Nmr δ -0.01 (s, 9H), 1.25-1.37 (m, 1H), 1.71-1 82 (m, 2H), 2.12-2.32 (m, 3H), 2.50-2.56 (m, 2H), 3.08-3.17 (m, 1H), 3.47-3.57 (m, 1H), 6.84 (br s, 1H); ir (KBr): 3300 (NH), 1730, 1700 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{20}NO_2F_3Si$: C, 48.80; H, 6.83; N, 4.74. Found: C, 48.57; H, 6.95; N, 4.72.

3-(3-Indolylacetyl)aminomethyl-5-trimethylsilylcyclohexanone (5e). mp 135.5-136.5 °C ($CHCl_3$). ^1H Nmr δ -0.08 (s, 9H), 1.14-1.29 (m, 1H), 1.53-1.62 (m, 2H), 2.02-2.39 (m, 5H), 2.95-3.04 (m, 1H), 3.20-3.30 (m, 1H), 3.74 (s, 2H), 5.83 (br s, 1H), 7.13-7.24 (m. 3H), 7.41 (d, J=7.9 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 8.60 (s, 1H); ^{13}C nmr δ -3.6, 21.4, 27.5, 33 4, 37.7, 41.8, 42.1, 44.0, 108.4, 111.7, 118.4, 120.0, 122.5, 124.0, 126.9, 136.5, 172.0, 212.4; ir (KBr): 3310 (NH), 1700, 1645 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_2Si$: C, 67.37; H, 7.92; N, 7.86. Found: C, 66.98; H, 7.83; N, 7.70.

5-Benzoylaminomethyl-2-cyclohexenone (6a). A solution of **5a** (6.06 g, 20 mmol) and $CuCl_2$ (8.07 g, 60 mmol) in DMF (140 ml) was heated at 60 °C for 50 min. After cooling to room temperature, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. Purification by column chromatography (hexane:AcOEt=1:2) gave **6a** (2.86 g, 62%). mp 112.0-112.5 °C (hexane-AcOEt). ^1H Nmr δ 2.18-2.32 (m, 2H), 2.42-2.64 (m, 3H), 3.39-3.49 (m, 1H), 3.54-3.64 (m, 1H), 6.06 (dd, J=2.6, 10.2 Hz, 1H), 6.26 (br s, 1H), 6.95-7.02 (m, 1H), 7.42-7.55 (m, 3H), 7.74-7.78 (m, 2H); ^{13}C nmr δ 29.8, 35.5, 41.9, 44.2, 127.0, 128.5, 129.6, 131.5, 134.3, 149.7, 168.1, 199.0; ir (KBr): 3280 (NH), 1665, 1633 (C=O) cm^{-1}. Anal. Calcd for

$C_{14}H_{15}NO_2$: C, 73.34; H, 6.60; N, 6.11. Found: C, 72.79; H, 6.90; N, 6.11.

5-Trifluoroacetylaminomethyl-2-clohexenone (6d). Oil. ^{1}H Nmr δ 2.13-2.29 (m, 2H), 2.37-2.59 (m, 3H), 3.31-3.53 (m, 2H), 6.07 (dd, J=2.3, 10.2 Hz, 1H), 6.78 (br s, 1H), 6.96-7.02 (m, 1H); ir (neat): 3310 (NH), 1720, 1680 (C=O) cm^{-1}.

5-(3-Indolylacetyl)aminomethyl-2-cyclohexenone (6e). Foam. ^{1}H Nmr δ 1.91-2.37 (m, 4H), 3.05-3.27 (m, 2H), 3.68-3.76 (m, 3H), 5.94-5.97 (m, 2H), 6.83-6.90 (m, 1H), 7.05-7.25 (m, 3H), 7.34-7.39 (m, 1H), 7.52 (d, J=7.6 Hz, 1H), 8.85 (s, 1H); ^{13}C nmr δ 29.6, 33.4, 35.4, 41.6, 43.7, 108.6, 111.6, 118.5, 120.1, 122.7, 123.9, 126.9, 129.7, 136.5, 149.3, 172.1, 198.9; ir (KBr): 3300 (NH), 1660 (C=O) cm^{-1}. Ms (70 ev) m/z (rel intensity) 282 (M^+; 12), 157 (10), 131 (13), 130 (100).

6-Benzyloxycarbonyl-6-azabicyclo[3.2.1]octan-3-one (7b). Oil. One to one mixture of invertomers in $CDCl_3$. ^{1}H Nmr δ 1.94 (d, J=12 Hz, 1H), 2.13-2.22 (m, 1H), 2.36 (ddd, J=2.2, 6.4, 17.3 Hz, 1H), 2.53-2.54 (br s, 2H), 2.74-2.94 (m, 2H), 3.38 (t, J=10.6 Hz, 1H), 3.46-3.55 (m, 1H), 4.34 and 4.42 (m, 1H), 5.04-5.18 (m, 2H), 7.34 (s, 5H); ^{13}C nmr δ 33.2, 34.1, 35.3, 35.9, 47.1, 47.7, 47.9, 48.0, 52.1, 52.4, 53.4, 53.5, 66.7, 66.9, 127.8, 127.9, 127.9, 128.0, 128.4, 128.5, 136.5, 136.6, 154.2, 208.6, 208.8; ir (neat): 1720, 1700 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.78; H, 6.81; N, 5.45.

6-Methoxycarbonyl-6-azabicyclo[3.2.1]octan-3-one (7c). Oil. One to one mixture of invertomers in $CDCl_3$. ^{1}H Nmr δ 1.93-2.00 (m, 1H), 2.08-2.21 (m, 1H), 2.36 (dd, J=2.3, 17.2 Hz, 1H), 2.45-2.61 (m, 2H), 2.73-2.90 (m, 2H), 3.28-3.38 (m, 1H), 3.40-3.52 (m, 1H), 3.67 and 3.70 (s, 3H), 4.30 and 4.40 (m, 1H); ^{13}C nmr δ 33.3, 34.2, 35.4, 36.0, 47.1, 47.7, 48.0, 48.1, 52.1, 52.3, 52.5, 52.5, 53 3, 53.5, 154.9, 208.7, 208.9; ir (neat): 1679, 1720 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.12; H, 7.32; N, 7.62.

6-(3-Indolylacetyl)-6-azabicyclo[3.2.1]octan-3-one (7e). mp 159-160 °C (AcOEt). Two to one mixture of invertomers in $CDCl_3$. ^{1}H Nmr δ 1 72 (s, 2H), 1.90-2.05 (m, 1H), 2.34-2.41 (m, 1H), 2.50-2.54 (m, 1H), 2.74 (s, 1H), 2.98-3.03 (m, 1H), 3.35-3.77 (m, 4H), 4.42 and 4.70 (br s, 1H), 7.01-7.22 (m, 3H), 7.35 (d, J=7.9 Hz), 7.55-7.60 (m, 1H), 8.32 (s, 1H); ^{13}C nmr δ 32.0, 34 5, 34.8, 46.6, 47.8, 52.8, 52.9, 108.3, 111.2, 118.3, 119.4, 122.1, 122.4, 127.1, 136.0, 170.0, 208.6, 31 8, 32.4, 36.5, 48.0, 48.2, 52.1, 54.3, 108.6, 119.6, 122.1, 122.5, 127.0, 169.8, 207.9; ir (KBr): 3310 (NH), 1710, 1630 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.80; H, 6.33; N, 9.75.

2,3-Epoxy-5-benzoylaminomethylcyclohexanone (8a). To a cooled (0 °C) solution of **7a** (458 mg, 2 mmol) in MeOH (20 ml) were added 35% H_2O_2 (0.26 ml, 3 mmol) and 6 M NaOH (0.167, 1 mmol). After 10 min stirring, the reaction was quenched by the addition of 0.1 M HCl (10 ml, 1 mmol) and Na_2SO_3 (252 mg, 2

mmol). Extraction with CH_2Cl_2 and purification by column chromatography (hexane:AcOEt=1:4) gave **8a** (430 mg, 88%). mp 116.0-116.5 °C (hexane-AcOEt). ^{1}H Nmr δ 1.71-1.81 (m, 1H), 1.88-1.98 (m, 1H), 2.36-2.47 (m, 2H), 2.62 (dd, J=4.6, 17.8 Hz, 1H), 3.25 (d, J=4.0 Hz, 1H), 3.28-3.38 (m, 1H), 3.41-3.51 (m, 1H), 3.59-3.61 (m, 1H), 6.41 (br s, 1H), 7.40-7.55 (m, 3H), 7.74-7.78 (m, 2H); ^{13}C nmr δ 27.4, 29.0, 40.6, 44.1, 54.7, 54.7, 126.9, 128.7, 131.7, 134.2, 167.9, 204.5; ir (KBr): 3290 (NH), 1707, 1616 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.17. Found: C, 68.19; H, 6.12; N, 5.77.

2,3-Epoxy-5-trifluoroacetylaminomethylcyclohexanone (8d). mp 90.5-91.5 °C (hexane-AcOEt). ^{1}H Nmr δ 1.67-2.00 (m, 2H), 2.34-2.49 (m, 2H), 2.51-2.62 (m, 1H), 3.21-3.41 (m, 3H), 3.64 (t, J=3.0 Hz, 1H), 7.09 (br s, 1H); ^{13}C nmr δ 27.2, 27.9, 40.3, 44.0, 54.4, 54.6, 115.8 (q, J=288 Hz), 157.9 (q, J=38 Hz), 203.9; ir (KBr): 3310 (NH), 1720 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{10}NO_3F_3$: C, 45.58; H, 4.25; N, 5.91. Found: C, 45.79; H, 4.42; N, 6.01.

2,3-Epoxy-5-(3-indolylacetyl)aminomethylcyclohexanone (8e). mp 117-118 °C (AcOEt). ^{1}H Nmr δ 1.42-1.52 (m, 1H), 1.59-1.70 (m, 1H), 2.04-2.18 (m, 2H), 2.29-2.36 (m, 1H), 3.00-3.14 (m, 3H), 3.46 (s, 1H), 3.72 (s, 2H), 5.95 (s, 1H), 7.09-7.27 (m, 3H), 7.38 (d, J=8.2 Hz, 1H), 7.50 (d, J=7.6 Hz), 1H), 8.86 (s, 1H); ^{13}C nmr δ 26.8, 27.9, 33.2, 40.3, 43.5, 54.3, 54.5, 108.1, 111.7, 118.3, 119.7, 122.2, 124.2, 126.9, 136.4, 172.5, 204.8; ir (KBr): 3400, 3300 (NH), 1710, 1650 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.05; H, 5.87; N, 9.34.

2,3-Epoxy-5-benzoylaminomethyl-1-methylenecyclohexane (9a). To a cooled (-40 °C) solution of methylenetriphenylphosphorane (1 mmol) in dry THF (5 ml) was added **8a** (123 mg, 0.5 mmol) in THF (2 ml). After stirring at -40 °C for 20 min and at room temperature for 30 min, saturated NH_4Cl solution was added. Extraction with ether and purification by chromatography (hexane:AcOEt=1:2) gave **9a** (108 mg, 89%). mp 108.0-108.5 °C (hexane-AcOEt). ^{1}H Nmr δ 1.58-1.67 (m, 1H), 1.78-2.08 (m, 2H), 2.22-2.29 (m, 1H), 2.43 (dd, J=1.3, 13.2 Hz, 1H), 3.26-3.48 (m, 4H), 5.19 (d, J=1.3 Hz, 1H), 5.34 (s, 1H), 6.12 (br s, 1H), 7.41-7.54 (m, 3H), 7.74-7.78 (m, 2H); ^{13}C nmr δ 28.4, 30.3, 32.8, 44.4, 53.6, 54.8, 118.5, 126.8, 128.6, 131.5, 134.5, 140.2, 167.7; ir (KBr): 3340 (NH), 1622 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.78; H, 7.02; N, 5.79.

2,3-Epoxy-5-(3-indolylacetyl)aminomethyl-1-methylenecyclohexane (9e). Foam. ^{1}H Nmr δ 1.35-1.79 (m, 3H), 1.98-2.05 (m, 1H), 2.15 (d, J=5.2 Hz, 1H), 2.95-3.02 (m, 1H), 3.07-3.14 (m, 1H), 3.29-3.33 (m, 2H), 3.75 (s, 2H), 4.90 (s, 1H), 5.16 (s, 1H), 5.72 (br s, 1H), 7.13-7.24 (m, 3H), 7.41 (d, J=7.9 Hz, 1H), 7.55 (d, J=7.6 Hz, 1H), 8.59 (br s, 1H); ^{13}C nmr δ 28.0, 30.0, 32.3, 33.4, 43.8, 53.5, 54.7, 108.9, 111.6, 118.1, 118.7, 120.2,

122.7, 123.8, 126.9, 136.5, 140.1, 171.8; ir (KBr): 3410, 3300 (NH), 1640 (C=O) cm^{-1}. Ms (70 ev) m/z (rel intensity) 296 (M+; 9), 157 (10), 131 (15), 130 (100).

2-Benzoyl-7-methylene-2-azabicyclo[2.2.2]octan-6-ol (11a). To a cooled (0 °C) solution of **9a** (98 mg, 0.4 mmol) in dry THF (10 ml) was added a THF solution of 1.04 M EtMgBr (1.16 ml, 1.2 mmol). After stirring at 0 °C for 0.5 h, the reaction was quenched with saturated NH_4Cl solution. Extraction with ether and purification by tlc (hexane:AcOEt=1:2) gave **11a** (86 mg, 88%). mp 146.0-147.0 °C (hexane-AcOEt). ca. 5:4 mixture of invertomers in $CDCl_3$. ^1H Nmr δ 1.74 (m, 1H), 2.09-2.68 (m, 5H), 3.09 (d, J=10.2 Hz, 1H), 3.33-3.60 (m, 1H), 3.94-3.99 (m, 1H), 4.63 (d, J=3.0 Hz, 1H), 4.93-5.06 (m, 2H), 7.37 and 7.39 (s, 5H); ^{13}C nmr δ 29.4, 34.9, 37.1, 53.5, 58.7, 71.0, 116.7, 126.5, 128.3, 129.6, 137.2, 145.3, 169.8, 30.9, 32.7, 36.8, 50.1, 60.5, 73.1, 117.6, 126.3, 128.5, 129.5, 137.3, 144.5, 169.8; ir (KBr): 3340 (OH), 1617 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.83; H, 7.06; N, 5.59.

2-(3-Indolylacetyl)-7-methylene-2-azabicyclo[2.2.2]octan-6-ol (11e). mp 219-221 °C (AcOEt). Ca. 2:1 mixture of invertomers in $CDCl_3$ containing a small amount of CD_3OD. ^1H Nmr ($CDCl_3$-CD_3OD) δ 1.61 (m, 1H), 2.05-2.14 (m, 2H), 2.23-2.27 (m, 1H), 2.42 (br s, 1H), 2.51-2.62 (m, 1H), 3.21-3.27 (m, 1H), 3.39-3.47 (m, 1H), 3.66-3.74 (m, 2H), 3.92-3.94 and 4.35-4.37 (m, 1H), 4.15-4.18 and 4.47-4.51 (m, 1H), 4.70-4.84 (m, 2H), 6.97-7.18 (m, 3H), 7.29 (d, J=7.6 Hz, 1H), 7.54-7.60 (m, 1H), 8.63 and 8.70 (s, 1H); ^{13}C nmr ($CDCL_3$-CD_3OD) δ 29.4, 31.8, 34.5, 37.1, 51.2, 58.4, 71.0, 108.5, 111.3, 117.1, 118.5, 119.3, 121.9, 123.1, 127.4, 136.2, 144.9, 170.2, 31.0, 31.8, 32.6, 36.7, 50.8, 59.7, 73.0, 109.3, 111.3, 117.9, 118.8, 119.4, 121.9, 122.9, 127.2, 136.2, 144.3, 169.7; ir (KBr): 3310 (OH), 1620 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.70; H, 6.65; N, 9.27.

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Received, 20th July, 1994