An Efficient Synthesis of 6-Substituted Aminohexahydro-1*H*-1,4-diazepines from 2-Substituted Aminopropenals

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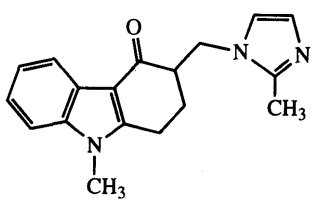
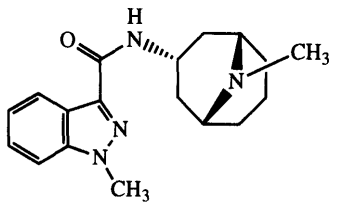
Swern oxidation of 2-substituted amino-1,3-propanediols 20a—d, 38, 41, and 42 smoothly proceeded to give the oxidative dehydration products, 2-substituted aminopropenals 17a—d, 43, 45 and 46, respectively. Reaction of the intriguing 2-substituted aminopropenals 17a—d with *N*-benzyl-N′-methyl- or *N*,*N*′-dimethylethylenediamine (12o or 12p) followed by $NaBH_4$ reduction of the iminium salt intermediates afforded the corresponding 6-substituted aminohexahydro-1*H*-1,4-diazepines 16 and 24—28. The similar ring formation of 1*H*-indazole derivatives 43 and 45 employing 12o directly furnished the 1*H*-indazole-3-carboxamide 4, which showed a potent serotonin-3 (5-HT_3) receptor antagonistic activity.

Key words hexahydro-1*H*-1,4-diazepine; 2-substituted aminopropenal; Swern oxidation; serotonin-3 (5-HT_3) receptor antagonist

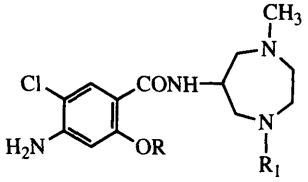
In recent years, a number of potent and selective serotonin-3 (5-HT_3) receptor antagonists, typified by granisetron and ondansetron, have been reported.[1] These compounds have been shown to be highly effective for the blockade of chemotherapy-induced emesis[2] and are in clinical trials for central nervous system disorders such as anxiety,[3] migraine,[4] and schizophrenia[5] and for the treatment of gastrointestinal motility disorders.[6] We have previously reported that the structurally novel benzamides **1**—**3** and the carboxamide **4** with a hexahydro-1*H*-1,4-diazepine ring in an amine moiety showed potent 5-HT_3 receptor antagonistic activity (Chart 1).[7] 6-Amino-1-benzyl-4-methyl- and 6-amino-1,4-dimethylhexahydro-1*H*-1,4-diazepines (**5**, **6**), which serve as the amine parts of compounds **1**—**4**, were prepared *via* the reaction of 1-benzenesulfonyl-2-bromomethylaziridine[8] (**7**), 2-phenyl-4-(*p*-toluenesulfonyloxymethyl)oxazoline[8] (**8**), β,β-dibromoisobutyric acid[8] (**9**), or tris(hydroxymethyl)nitromethane[9] (**10**) with *N*-benzyl-*N*′-methylethylenediamine (**12o**) or *N*,*N*′-dimethylethylenediamine (**12p**). However, the methods afford low overall yields of **5** and **6**. On the other hand, reduction of the 2,3-diaminopropionate **13**, which was obtained from methyl 2-(*tert*-butoxycarbonylamino)propenate (**11**) and **12o**, with diisobutylaluminum hydride (DIBAL-H), followed by further reduction of the iminium salt **15**, derived from the aldehyde **14**, with $NaBH_4$ produced 1-benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepine (**16**) in a good yield.[8] Acid hydrolysis of the resultant **16** afforded the amine **5** (Chart 2). Conceptually, in the original formation of a hexahydro-1*H*-1,4-diazepine ring, treatment of 2-substituted aminopropenals instead of **11** with **12o** followed by $NaBH_4$ reduction could directly give the hexahydro-1*H*-1,4-diazepine derivatives. For the success of this approach, preparation of the intriguing 2-substituted aminopropenals is essential. To our knowledge, there has been no report on the synthesis of 2-substituted aminopropenals thus far. Reduction of **11** with DIBAL-H was first surveyed. However, only a complex mixture was obtained. Tanaka *et al.*[10] reported that oxidation of 2-(2-nitrophenyl)-1,3-propanediol (**18**) with a combination of 1,3-dicyclohexylcarbodiimide



ondansetron



granisetron



1; R = C_2H_5, R_1 = CH_3
2; R = CH_3, R_1 = CH_2Ph
3; R = C_2H_5, R_1 = CH_2Ph

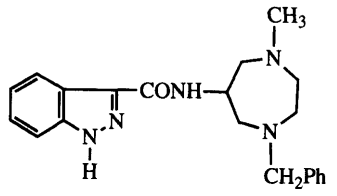


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Chart 1

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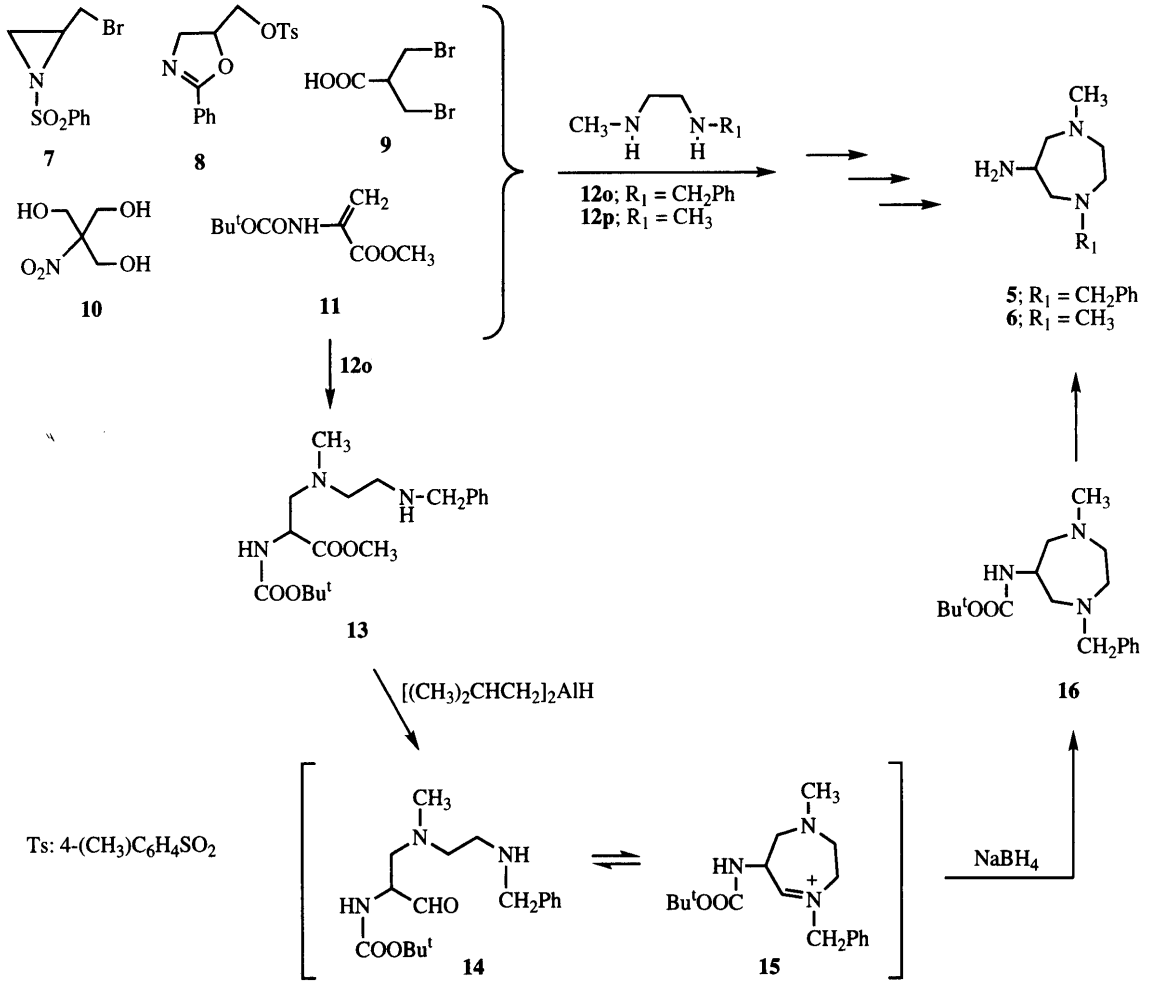


Chart 2

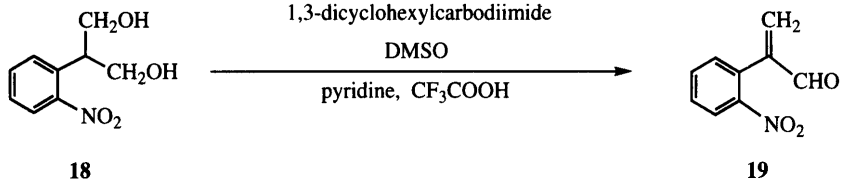


Chart 3

(DCC) and dimethyl sulfoxide (DMSO) in the presence of pyridine and trifluoroacetic acid gave the oxidative dehydration product, 2-(2-nitrophenyl)propenal (**19**), in 97% yield (Chart 3). Thus, we expected that DMSO oxidation of 2-substituted 1,3-propanediols would afford 2-substituted aminopropenals. Herein we describe an efficient synthesis of 2-substituted aminopropenals and formation of a hexahydro-1*H*-1,4-diazepine ring featuring the reaction of 2-substituted aminopropenals with the ethylenediamine **12o** or **12p**.

Synthesis of 2-Substituted Aminopropenals from 2-Substituted Amino-1,3-propanediols For the examination of the reactivity of Swern oxidation, 2-amino-1,3-propanediol derivatives with different protecting groups were prepared as starting materials; treatment of 2-amino-1,3-propanediol (**21**) with acetic anhydride, di-*tert*-butyl dicarbonate, benzoyl chloride, and benzyl chloroformate gave *N*-(1,3-propanediol-2-yl)acetamide (**20a**), 2-(*tert*-butoxycarbonylamino)-1,3-propanediol (**20b**), *N*-(1,3-propanediol-2-yl)benzamide (**20c**), and 2-benzyloxycarbonylamino-1,3-propanediol (**20d**), respectively. Compound **20d** was also obtained by reduction of *N*-(benzyloxycarbonyl)-DL-serine methyl ester[11] (**22**) with $LiBH_4$. As 2-substituted aminopropenals may be unstable, we selected the oxalyl chloride version of the Swern procedure[12] for the oxidation. First, *N*-(1,3-propanediol-2-yl)acetamide (**20a**) was subjected to oxidation using oxalyl chloride, DMSO, and Et_3N at $-70\,^{\circ}C$ to give the expected oxidative dehydration product, 2-acetylaminopropenal (**17a**), as a solid in 65% yield. In the case of this oxidation, a trace of the known bisaldehyde of **20a**, acetylaminomalonaldehyde[13] (**23**), was detected by TLC analysis. The structure of **17a** was supported by the following results. The ^{1}H-NMR spectrum in $CDCl_3$ solution was similar to that of the commercial methyl 2-acetamidoacrylate; one methylene proton signal was observed at δ

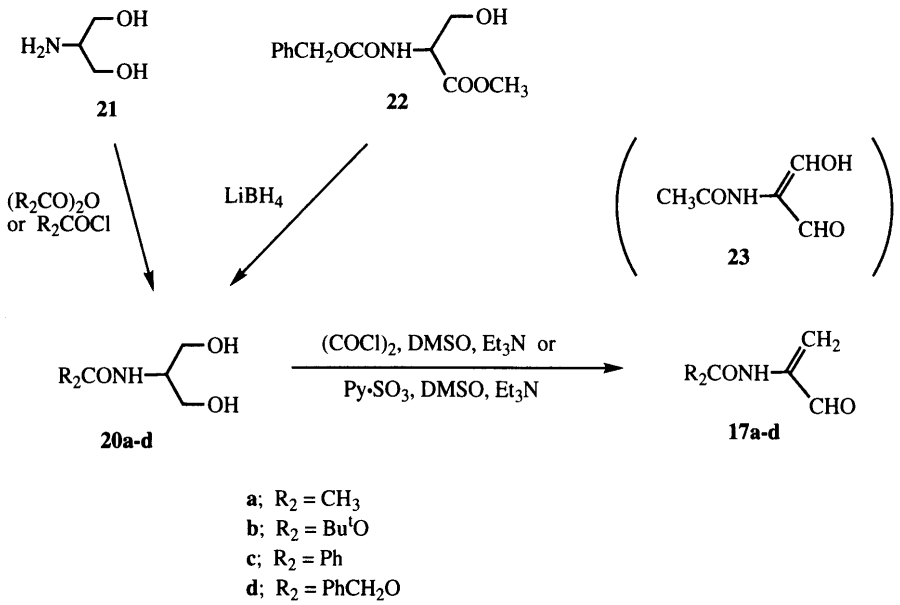
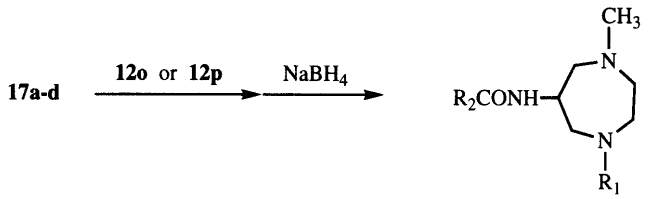


Chart 4

5.57 as a double doublet with coupling constants of 1.3 and 0.2 Hz owing to its spin–spin coupling to NH and geminal proton couplings, respectively. Addition of D_2O changed the double doublet pattern into a doublet with a coupling constant of 0.2 Hz. The signal of the other methylene proton appeared as a doublet centered at δ 7.15 with a coupling constant of 0.2 Hz. MS measurement also supported the proposed structure. Similarly, Swern oxidation of **20b—d** reproducibly proceeded to afford the corresponding propenal derivatives **17b—d**,[14] respectively, as oils in moderate yields. Several protecting groups had no effect on the yield of the propenal derivatives. Finally, in an attempt to find a viable method for oxidation of the 1,3-propanediols, we investigated various oxidative conditions such as DMSO/pyridine sulfur trioxide in the presence of Et_3N at room temperature,[15] DMSO/trifluoroacetic anhydride at $-50\,^{\circ}C$,[16] DMSO/DCC in the presence of pyridine and trifluoroacetic acid at room temperature for 4 h,[10] and manganase dioxide in acetone at room temperature for 20 h.[17] DMSO oxidation using pyridine sulfur trioxide resulted in a lower yield of the propenals and no detection of the bisaldehydes on TLC, presumably because of the thermal instability of the products in solution. The other methods, however, did not produce the propenals and/or bisaldehydes (Chart 4).

Synthesis of 6-Substituted Aminohexahydro-1*H*-1,4-diazepines and 5-HT$_3$ Receptor Antagonist from 2-Substituted Aminopropenals As a preliminary experiment aimed at formation of a 6-substituted aminohexahydro-1*H*-1,4-diazepine ring, reaction of **17a—d** with **12o** and **12p** was first examined. Brief treatment of **17a** with **12o** at *ca.* 5 °C followed by $NaBH_4$ reduction provided the reported *N*-(1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-acetamide[18] (**24**) in 35% yield. The reactions of **17a—d** with **12o** and/or **12p** under similar conditions also gave the 6-substituted aminohexahydro-1*H*-1,4-diazepine analogs (**16**, **25—28**) in 30—60% yield (Chart 5). As anticipated, the hexahydro-1*H*-1,4-diazepine derivatives were obtained from 2-substituted aminopropenals and the

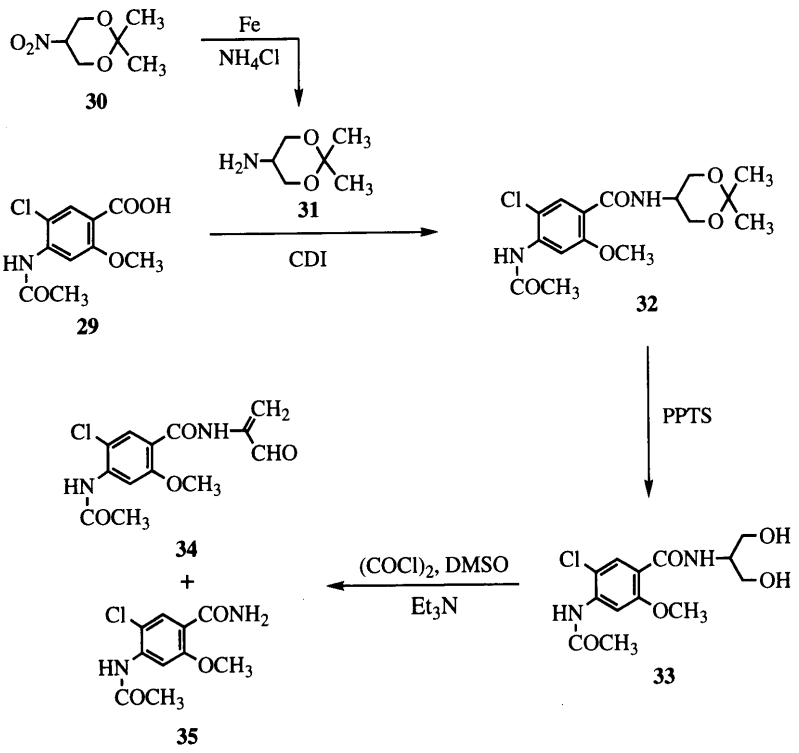


16; $R_1 = CH_2Ph$, $R_2 = Bu^tO$
24; $R_1 = CH_2Ph$, $R_2 = CH_3$
25; $R_1 = R_2 = CH_3$
26; $R_1 = CH_2Ph$, $R_2 = Ph$
27; $R_1 = CH_3$, $R_2 = Ph$
28; $R_1 = CH_2Ph$, $R_2 = PhCH_2O$

Chart 5

ethylenediamines **12o** and **12p**, although the yields were not satisfactory.

On the basis of the results obtained above, we next turned our attention to the straightforward synthesis of the benzamides **1—3** and the carboxamide **4** with potent 5-HT$_3$ receptor antagonistic activity; it was expected that the treatment of the pivotal propenals having 4-acetylamino-5-chloro-2-alkoxybenzoyl and 1*H*-indazole-3-carbonyl groups with **12o** would give the desired amides **1—3** and **4**. The synthesis of 2-(4-acetylamino-5-chloro-2-methoxybenzoyl)aminopropenal (**34**) was performed as follows. Condensation of 4-acetylamino-5-chloro-2-methoxybenzoic acid[19] (**29**) with **21** gave the polar products, including the desired **33**, but the purification of **33** proved to be difficult. The benzoic acid **29** was allowed to react with 5-amino-2,2-dimethyl-1,3-dioxane (**31**), which was obtained by reduction of 5-nitro-2,2-dimethyl-1,3-dioxane[20] (**30**) with Fe and ammonium chloride, in the presence of *N*,*N*′-carbonyldiimidazole (CDI), giving the benzamide **32** in 50% yield. The subsequent treatment of **32** with pyridinium *p*-toluenesulfonate (PPTS) furnished the 1,3-propanediol **33**. To obtain the propenal **34** as a key intermediate, Swern oxidation of **33** was carried out.



CDI; *N,N'*-carbonyldiimidazole
PPTS; pyridinium *p*-toluenesulfonate

Chart 6

To our disappointment, however, the crude propenal **34** was isolated as a powder in only *ca.* 10% yield, along with the unexpected elimination product **35** in 32% yield. Furthermore, recrystallization of the crude **34** resulted in an increase of the by-product **35**. The mechanism of transformation of **34** into **35** is not clear (Chart 6). As a result, we gave up our attempts to synthesize **1**—**3** from the corresponding 2-propenals.

We next examined the synthetic route to the 1*H*-indazole-3-carboxamide **4** from the 2-propenal counterpart. Reaction of diindazolo[2,3-*a*: 2',3'-*d*]pyrazine-7,14-dione[21] (**36**), which is the dimer of 1*H*-indazole-3-carboxylic acid (**39**), with **21** furnished the 1*H*-indazole-3-carboxamide **37** in a good yield. Swern oxidation of the 1-acetyl analogue of **37** gave only a complex mixture. This may be due to ready cleavage of the acetyl group under the conditions used. We then tried the ethoxycarbonyl group as a protecting group. The 1-ethoxycarbonyl-1*H*-indazole **38** was prepared by reaction of **37** with ethyl chloroformate. In this reaction, the formation of the regioisomer, 2-ethoxycarbonyl-2*H*-indazole counterpart, was not detected in the ^{1}H-NMR spectrum of the crude product, presumably owing to the steric hindrance at the 3-position of the 1*H*-indazole ring. Swern oxidation of the resultant **38** furnished the propenal **43** as stable white crystals in 87% yield. The corresponding bisaldehyde and the elimination product were not detected by TLC analysis. The reason for the different products of Swern oxidation remains unclear. Treatment of **43** with **12o** followed by $NaBH_4$ reduction gave the 1*H*-indazole-3-carboxamide **4** in only 23% yield, without isolation of the 1-ethoxycarbonyl-1*H*-indazole-3-carboxamide **44**. To improve the yield of **4**, the ethoxycarbonyl group of **43** was changed to a benzyloxycarbonyl or a methoxymethyl group. As an alternative synthesis, condensation of **39**[22] with the amine **31** using CDI afforded the carboxamide **40**, which was treated with benzyl chloroformate and chloromethyl methyl ether–potassium *tert*-butoxide, followed by acid hydrolysis of 1,3-dioxane ring, to produce the 1-benzyloxycarbonyl- and 1-methoxymethyl-1*H*-indazole-3-carboxamides **41** and **42**, respectively, in good yields. Swern oxidation of **41** and **42** gave the propenals **45** and **46**, respectively, as stable solids without detection of the corresponding bisaldehyde on TLC. The reaction of **45** with **12o** followed by $NaBH_4$ reduction directly provided **4** in a good yield without isolation of the 1-benzyloxycarbonyl-1*H*-indazole-3-carboxamide **47**. On the other hand, the similar reaction of **46** with **12o** gave the precursor of **4**, the 1-methoxymethyl-1*H*-indazole-3-carboxamide **48**, in 78% yield. Acid hydrolysis of **48** afforded the desired 1*H*-indazole-3-carboxamide **4** (Chart 7). As a result, the use of benzyloxycarbonyl group appeared to be superior to the use of the ethoxycarbonyl or methoxymethyl group in terms of the overall yield of **4** and simplicity of operation.

In conclusion, we have succeeded in developing a novel synthesis of 6-substituted amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepines, including a potent 5-HT_3 receptor antagonist, the 1*H*-indazole-3-carboxamide **4**, by employing the reaction of 2-substituted amino-2-propenals with *N*-benzyl-*N'*-methyl- or *N,N'*-dimethylethylenediamine. The pivotal 2-substituted aminopropenals

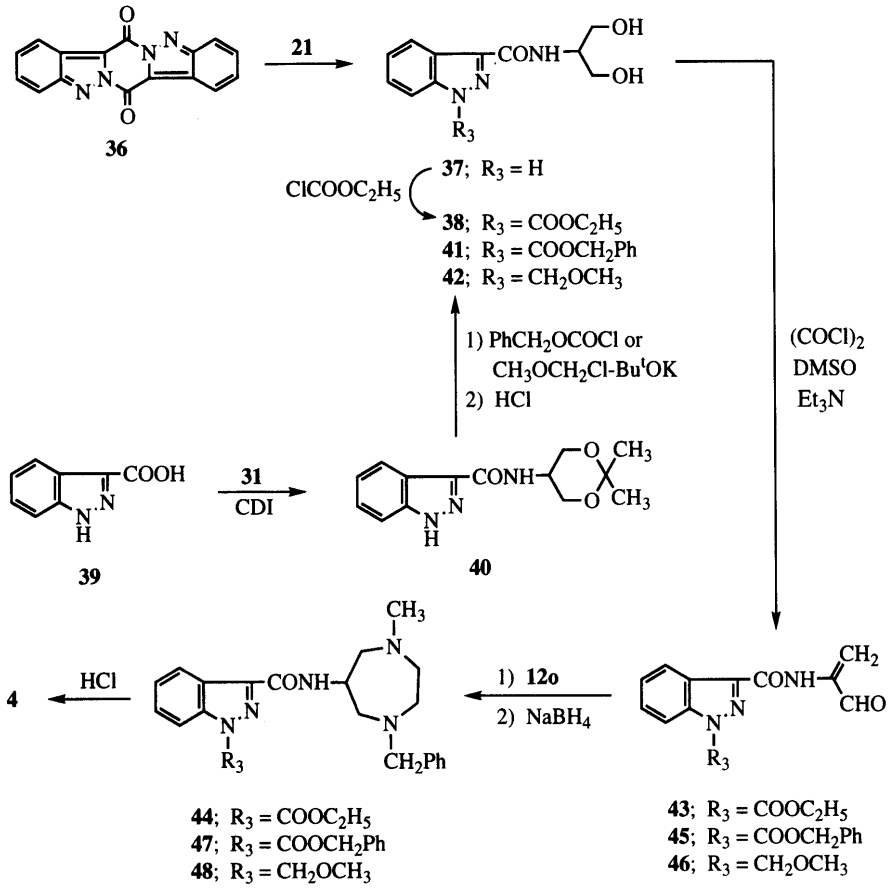


Chart 7

were obtained from 2-substituted amino-1,3-propanediols by use of Swern oxidation.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 spectrometer and a Shimadzu FTIR-8200PC spectrometer. Electron ionization (EI) and secondary ion (SI) mass spectra were obtained on a JEOL JMS D-300 or a Hitachi M-80-B spectrometer. ^{1}H-NMR spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer unless otherwise specified. ^{1}H-NMR spectra (300 MHz) were recorded on a Varian XL-300 spectrometer. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck Silica gel 60 (70—230 mesh) was used for column chromatography.

***N*-(1,3-Propanediol-2-yl)acetamide (20a)** Acetic anhydride (44.9 g, 0.44 mol) was added dropwise to a mixture of 2-amino-1,3-propanediol (**21**, 36.4 g, 0.40 mol) and pyridine (200 ml) at *ca.* 0 °C. The reaction mixture was stirred at room temperature for 1 h and concentrated to dryness. The residual oil was dissolved in ethyl acetate (AcOEt) and then stirred at *ca.* 5 °C. The resulting precipitates were collected by filtration and washed with AcOEt to give 41.1 g (77%) of **20a** as a white powder. An analytical sample was obtained by recrystallization from MeOH–AcOEt, mp 86—87 °C [lit.[23] mp 89—90 °C (MeOH–AcOEt)]. ^{1}H-NMR (DMSO-d_6) δ: 1.82 (s, 3H, CH_3CO), 3.38 (d, J=7.5 Hz, 4H, $CH_2OH \times 2$), 3.67 (m, 1H, 2-CH), 4.59 (t, J=7.5 Hz, 2H, $CH_2OH \times 2$), 7.53 (br d, J=8 Hz, 1H, CONH). SI-MS *m/z*: 134 (MH^+), 116. IR (KBr) ν cm^{-1}: 3292, 1657, 1560. *Anal.* Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.14; H, 8.50; N, 10.48.

2-(*tert*-Butoxycarbonylamino)-1,3-propanediol (20b) Di-*tert*-butyl dicarbonate (48.0 g, 0.22 mol) was added dropwise to a solution of **21** (18.2 g, 0.20 mol) in MeOH (300 ml) kept at 15 °C. The mixture was stirred at room temperature for 4 h and concentrated to dryness. The residual solid was recrystallized from acetone–hexane to give 34.2 g (90%) of **20b** as colorless crystals, mp 79—81 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.37 (s, 9H, $(CH_3)_3C$), 3.30—3.45 (m, 5H), 4.50 (t, J=5 Hz, 2H, $CH_2OH \times 2$), 6.29 (br d, J=6 Hz, 1H, CONH). SI-MS *m/z*: 192 (MH^+), 136. IR (KBr) ν cm^{-1}: 3323, 1688, 1537. *Anal.* Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.41; H, 8.94; N, 7.38.

***N*-(1,3-Propanediol-2-yl)benzamide (20c)** Benzoyl chloride (46.5 g, 0.33 mol) was added dropwise to a stirred mixture of **21** (27.3 g, 0.30 mol), K_2CO_3 (45.5 g, 0.33 mol), and H_2O (200 ml) at *ca.* 5 °C. The mixture was stirred at the same temperature for 1.5 h and then concentrated. The resulting precipitates were collected by filtration to give 43.4 g (74%) of **20c** as a white powder. An analytical sample was obtained by recrystallization from acetone–hexane, mp 118—120 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.53 (d, J=6.5 Hz, 4H, $CH_2OH \times 2$), 3.90 (m, 1H, 2-CH), 4.66 (t, J=7 Hz, 2H, $CH_2OH \times 2$), 7.38—7.59, 7.81—7.91 (m, 5H, arom. H), 7.95 (br d, J=7 Hz, 1H, CONH). SI-MS *m/z*: 196 (MH^+). IR (KBr) ν cm^{-1}: 3298, 1638, 1551. *Anal.* Calcd for $C_{10}H_{13}NO_3 \cdot 0.4H_2O$: C, 59.34; H, 6.87; N, 6.92. Found: C, 59.34; H, 6.51; N, 6.91.

2-Benzyloxycarbonylamino-1,3-propanediol (20d). From 2-Amino-1,3-propanediol (21) Benzyl chloroformate (56.3 g, 0.33 mol) was added dropwise to a stirred mixture of **21** (27.3 g, 0.30 mol), K_2CO_3 (45.5 g, 0.33 mol), and H_2O (200 ml) at *ca.* 5 °C. The mixture was stirred at the same temperature for 1 h and then concentrated. AcOEt was added to the residue, and the insoluble materials were filtered off. The filtrate was evaporated to leave a solid, which was triturated with Et_2O to give 20.3 g (30%) of **20d** as a white powder. An analytical sample was obtained by recrystallization from acetone–hexane, mp 93—96 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.25—3.53 (m, 5H), 4.57 (t, J=7 Hz, 2H, $CH_2OH \times 2$), 5.02 (s, 2H, OCH_2Ph), 6.86 (d, J=7 Hz, 1H, CONH), 7.25—7.40 (m, 5H, arom. H). SI-MS *m/z*: 226 (MH^+), 194, 150, 108. IR (KBr) ν cm^{-1}: 3280, 1675, 1530. *Anal.* Calcd for $C_{11}H_{15}NO_4 \cdot 0.25H_2O$: C, 57.51; H, 6.80; N, 6.10. Found: C, 57.76; H, 6.63; N, 6.39.

From *N*-(Benzyloxycarbonyl)-DL-serine Methyl Ester (22) A stirred mixture of **22**[11] (2.5 g, 9.9 mmol), LiCl (0.85 g, 20 mmol), $NaBH_4$ (0.76 g, 20 mmol), and tetrahydrofuran (THF, 20 ml) was treated dropwise with EtOH (40 ml) at *ca.* 5 °C. The mixture was stirred at room temperature for 18 h and adjusted to a pH of about 5 with 10% aqueous citric acid solution. The reaction mixture was concentrated, and then $CHCl_3$ (50 ml) and water (50 ml) were added. The insoluble materials were

Table 1. Physicochemical and Spectral Data for the 2-Substituted Aminopropenals

No.	Yield[a] (%)	mp (°C) (Solv.)	Formula	Analysis Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1}) ν
17b	48	Oil	$C_8H_{13}NO_3$	SI-MS: 172 (MH^+)			1.49 (s, 9H, $(CH_3)_3C$), 5.40 (d, J=1.0 Hz, 1H, C=C$\underline{H}_2$), 6.72 (s, 1H, C=C$\underline{H}_2$), 6.99 (br s, 1H, CONH), 9.15 (s, 1H, CHO)	1734, 1693, 1516 (neat)
17c	55	Oil	$C_{10}H_9NO_2$	EI-MS: 175 (M^+)			5.67 (d, J=1.3 Hz, 1H, C=C$\underline{H}_2$), 7.15 (s, 1H, C=C$\underline{H}_2$), 7.72 (br s, 1H, CONH), 7.38—7.66, 7.82—7.93 (m, 5H, arom. H), 9.27 (s, 1H, CHO)	1725, 1665, 1510 (neat)
17d	51	Oil	$C_{11}H_{11}NO_3$	SI-MS: 206 (MH^+)			5.18 (s, 2H, OC$\underline{H}_2$Ph), 5.42 (d, J=1.3 Hz, 1H, C=C$\underline{H}_2$), 6.80 (s, 1H, C=C$\underline{H}_2$), 7.20 (br s, 1H, CONH), 7.30—7.40 (m, 5H, arom. H), 9.17 (s, 1H, CHO)	1730, 1680, 1510 (neat)
43	87	150—152 (MeOH)	$C_{14}H_{13}N_3O_4$	58.53 (58.45	4.56 4.46	14.63 14.56)	1.55 (t, J=7 Hz, 3H, $CH_2C\underline{H}_3$), 4.64 (q, J=7 Hz, 2H, $C\underline{H}_2CH_3$), 5.74 (d, J=1.3 Hz, 1H, C=C$\underline{H}_2$), 7.38 (s, 1H, C=C$\underline{H}_2$), 7.47 (dd, J=8, 8 Hz, 1H, indazole 5-H), 7.62 (dd, J=8, 8 Hz, 1H, indazole 6-H), 8.28 (d, J=8 Hz, 1H, indazole 7-H), 8.41 (d, J=8 Hz, 1H, indazole 4-H), 9.30 (s, 1H, CHO), 9.38 (br s, 1H, CONH)	1755, 1680, 1537 (KBr)
45	77	150—152 (EtOH)	$C_{19}H_{15}N_3O_4$	65.32 (65.08	4.33 4.10	12.03 11.95)	5.60 (s, 2H, OC$\underline{H}_2$Ph), 5.74 (dd, J=0.6, 1.3 Hz, 1H, C=C$\underline{H}_2$), 7.35 (d, J=0.6 Hz, 1H, C=C$\underline{H}_2$), 7.39—7.70 (m, 7H, indazole 5-H, 6-H, arom. H), 8.24 (ddd, J=1.0, 1.0, 9.0 Hz, 1H, indazole 7-H), 8.40 (ddd, J=1.0, 1.0, 9.0 Hz, 1H, indazole 4-H), 9.29 (s, 1H, CHO), 9.40 (br s, 1H, CONH)	1759, 1680, 1537 (KBr)
46	61	105—106 (MeOH)	$C_{13}H_{13}N_3O_3$	60.23 (60.27	5.05 5.33	16.21 15.93)	3.35 (s, 3H, $CH_2OC\underline{H}_3$), 5.68 (d, J=1.3 Hz, 1H, C=C$\underline{H}_2$), 5.88 (s, 2H, $C\underline{H}_2OCH_3$), 7.38 (s, 1H, C=C$\underline{H}_2$), 7.39 (dd, J=8, 8 Hz, 1H, indazole 5-H), 7.50 (dd, J=8, 8 Hz, 1H, indazole 6-H), 7.64 (d, J=8 Hz, 1H, indazole 7-H), 8.40 (d, J=8 Hz, 1H, indazole 4-H), 9.30 (s, 1H, CHO), 9.38 (br s, 1H, CONH)	1682, 1531 (KBr)

a) Based on compounds **20b—d**, **38**, **41**, **42**.

collected by filtration to give 1.3 g (58%) of **20d**, which was identical with the sample obtained above, by comparison of the IR and ^{1}H-NMR spectra.

2-Acetylaminopropenal (17a) A mixture of DMSO (35 ml) and CH_2Cl_2 (35 ml) was added dropwise to a solution of oxalyl chloride (9.5 g, 75 mmol) in CH_2Cl_2 (60 ml) at −70 °C. The mixture was stirred at the same temperature for 10 min, and then a solution of **20a** (6.7 g, 50 mmol) in a mixture of DMSO (60 ml) and CH_2Cl_2 (30 ml) was added dropwise. Stirring was continued at −70 °C for 20 min, then Et_3N (34 ml) was added dropwise. The whole was stirred at the same temperature for 20 min, gradually warmed to −15 °C, and quenched by addition of water (150 ml). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic solution was washed successively with 10% aqueous citric acid solution, water, and brine. The solvent was evaporated to give 3.7 g (65%) of **17a** as a pale yellow viscous oil, which solidified upon standing. An analytical sample was obtained by trituration from Et_2O–hexane, mp 49—50 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3H, $COCH_3$), 5.57 (dd, J=1.3, 0.2 Hz, 1H, C=C$\underline{H}_2$), 7.15 (d, J=0.2 Hz, 1H, C=C$\underline{H}_2$), 7.68 (br s, 1H, CONH, disappeared with D_2O), 9.15 (s, 1H, CHO). ^{1}H-NMR ($CDCl_3+D_2O$) δ: 5.57 (d, J=0.2 Hz, 1H, C=CH_2), 7.15 (d, J=0.2 Hz, 1H, C=CH_2). EI-MS m/z: 113 (M^+). IR (KBr) ν cm^{-1}: 3368, 1682, 1539, 1289. *Anal.* Calcd for $C_5H_7NO_2 \cdot 0.25H_2O$: C, 51.06; H, 6.43; N, 11.91. Found: C, 50.75; H, 6.16; N, 11.72.

In a similar manner to that described above, 2-(*tert*-butoxycarbonyl)-amino-, 2-benzoylamino-, and 2-benzyloxycarbonylaminopropenals (**17b—d**) were obtained from **20b—d**, respectively, as pale yellow viscous oils. The chemical data for these compounds are summarized in Table 1.

DMSO/Pyridine Sulfur Trioxide/Et_3N Oxidation of 20b A solution of pyridine sulfur trioxide (98%, 40.8 g, 0.25 mol) in DMSO (100 ml) was added dropwise to a mixture of **20b** (8.0 g, 42 mmol), Et_3N (55.0 g, 0.54 mol), and DMSO (100 ml) kept at *ca.* 20 °C. The reaction mixture was stirred at room temperature for 0.5 h. The Et_3N was evaporated, and the resulting solution was poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% aqueous citric acid solution, water, and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with AcOEt/hexane = 1/1 to give 1.8 g (25%) of **17b**. This compound was identical with the sample obtained above, based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)acetamide (24)** *N*-Benzyl-*N'*-methylethylenediamine[24] (**12o**, 3.8 g, 23 mmol) was added dropwise to a stirred solution of **17a** (2.6 g, 23 mmol) in MeOH (30 ml) at *ca.* 5 °C. After 5 min, $NaBH_4$ (2.2 g, 58 mmol) was added portionwise at 5—10 °C. The mixture was stirred at room temperature for 2 h and then concentrated to dryness. The residue was dissolved in AcOEt and washed successively with water and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$/MeOH = 15/1 to give 2.1 g (35%) of **24** as an oil. This compound was identical with the sample obtained in the alternative synthesis,[18] based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

1-Benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepine (16) In a similar manner to that described above, **16** was obtained from **17b** and **12o** in 44% yield as an oil. This compound was identical with the sample obtained in the alternative synthesis,[8] based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

***N*-(1,4-Dimethylhexahydro-1*H*-1,4-diazepin-6-yl)acetamide (25)** In a similar manner to that described for **24**, **25** was obtained from **17a** and **12p** in 58% yield as an oil. This compound was identical with the sample obtained in the alternative synthesis,[9] based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)benzamide (26)** In a similar manner to that described for **24**, **26** was obtained from **17c** and **12o** in 48% yield as an oil. This compound was identical with the sample obtained in the alternative synthesis,[8] based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

***N*-(1,4-Dimethylhexahydro-1*H*-1,4-diazepin-6-yl)benzamide (27)** In a similar manner to that described for **24**, **27** was obtained from **17c** and

12p in 33% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (6H, s, $NCH_3 \times 2$), 2.45—2.98 (8H, m), 4.32 (1H, m, 6-CH), 7.39—7.60, 7.79—7.90 (6H, m, arom. H, CONH). EI-MS *m/z*; 247 (M^+). IR (neat) ν cm^{-1}: 3320, 1645, 1537.

1-Benzyl-6-benzyloxycarbonylamino-4-methylhexahydro-1*H*-1,4-diazepine (28) In a similar manner to that described for **24**, **28** was obtained from **17d** and **12o** in 46% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3N), 2.40—2.96 (m, 8H), 3.49 (d, J=12 Hz, 1H, CH_2Ph), 3.58 (d, J=12 Hz, 1H, CH_2Ph), 3.83 (m, 1H, 6-CH), 5.07 (s, 2H, OCH_2Ph), 7.71 (d, J=8 Hz, 1H, CONH), 7.15—7.44 (m, 10H, arom. H). EI-MS *m/z*: 353 (M^+), 202 ($M^+ - PhCH_2OCONH_2$). IR (neat) ν cm^{-1}: 3390, 2940, 1715, 1480.

5-Amino-2,2-dimethyl-1,3-dioxane (31) A mixture of 2,2-dimethyl-5-nitro-1,3-dioxane[20] (**30**, 230 g, 1.4 mol), Fe (powder, 640 g, 11.5 mol), ammonium chloride (153 g, 2.9 mol), and 50% aqueous EtOH (7000 ml) was heated to reflux for 2 h and then cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated. The resulting aqueous solution was washed with $CHCl_3$ (400 ml × 2), basified with excess K_2CO_3 (*ca.* 700 g), and extracted with $CHCl_3$ (500 ml × 2). The extract was concentrated to leave a pale brown oil, which was distilled to give 138 g (74%) of **31**[25] as a colorless oil, bp 56—58 °C (2 mmHg) [lit.[25a] mp 170—171 °C (acetone–H_2O)]. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (s, 2H, NH_2), 1.43 (s, 6H, $CH_3 \times 2$), 2.85 (m, 1H, 5-CH), 3.55 (dd, J=5, 12 Hz, 2H, 4-C$\underline{H}_2$, 6-C$\underline{H}_2$), 4.03 (dd, J=3, 12 Hz, 2H, 4-C$\underline{H}_2$, 6-C$\underline{H}_2$). SI-MS *m/z*: 132 (MH^+). IR (neat) ν cm^{-1}: 3350, 2980, 2930, 2860, 1370, 1198, 1070. *Anal.* Calcd for $C_6H_{13}NO_2 \cdot 0.5H_2O$: C, 51.41; H, 10.07; N, 9.99. Found: C, 51.41; H, 9.85; N, 9.91.

4-Acetylamino-5-chloro-*N*-(2,2-dimethyl-1,3-dioxan-5-yl)-2-methoxybenzamide (32) A mixture of 4-acetylamino-5-chloro-2-methoxybenzoic acid[19] (**29**, 20.0 g, 82 mmol), CDI (16.0 g, 99 mmol), and dimethylformamide (DMF) (200 ml) was stirred at room temperature for 1 h. Compound **31** (11.3 g, 86 mmol) was added, and the whole was stirred at room temperature for an additional 18 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed successively with 10% aqueous NaOH solution, water, and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$/MeOH = 10/1 to give 14.6 g (50%) of **32** as a colorless oil. The oil was crystallized from toluene, mp 141.5—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46, 1.52 (each s, each 3H, 2-CH_3), 2.17 (s, 3H, $COCH_3$), 4.03 (s, 3H, OCH_3), 3.72—4.25 (m, 5H), 8.02 (s, 1H, NHCO), 8.21 (s, 1H, arom. 3-H), 8.34 (s, 1H, arom. 6-H), 8.82 (d, J=8 Hz, 1H, CONH). SI-MS *m/z*: 357 (MH^+), 352, 299. IR (KBr) ν cm^{-1}: 3398, 1701, 1649, 1506, 1242. *Anal.* Calcd for $C_{16}H_{21}ClN_2O_5$: C, 53.86; H, 5.93; Cl, 9.94; N, 7.85. Found: C, 53.80; H, 6.08; Cl, 9.75; N, 7.87.

4-Acetylamino-5-chloro-*N*-(1,3-dihydroxy-2-propyl)-2-methoxybenzamide (33) A mixture of **32** (13.7 g, 38 mmol), PPTS (2.5 g, 9.9 mmol), and MeOH (50 ml) was stirred at room temperature for 2 d. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$/MeOH = 7/1 to give a solid. The solid was recrystallized from AcOEt to afford 9.9 g (81%) of **33**, mp 151—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.17 (s, 3H, $COCH_3$), 3.40—3.61 (m, 4H, C$\underline{H}_2$OH × 2), 3.87 (s, 3H, OCH_3), 3.90 (m, 1H, 2-CH), 4.80 (t, J=11 Hz, 2H, $CH_2O\underline{H} \times 2$), 7.82 (s, 1H, arom. 3-H), 7.89 (s, 1H, arom. 6-H), 8.13 (d, J=8 Hz, 1H, NHCO), 9.57 (s, 1H, NHCO). SI-MS *m/z*: 317 (MH^+), 226. IR (KBr) ν cm^{-1}: 3356, 1684, 1636, 1541, 1070. *Anal.* Calcd for $C_{13}H_{17}ClN_2O_5$: C, 49.30; H, 5.41; Cl, 11.19; N, 8.84. Found: C, 49.21; H, 5.37; Cl, 11.25; N, 8.81.

Swern Oxidation of 33 In a similar manner to that described for **17a**, **33** (2.9 g, 9.2 mmol) was treated with DMSO, oxalyl chloride, and Et_3N to give a mixture of **34** and **35** (*ca.* 1.0 g) as a solid. The solid was washed with iso-PrOH to afford 0.3 g (*ca.* 10%)[26] of **34** as a powder. The filtrate was concentrated to dryness to give 0.7 g (32%) of **35** as a solid. **34**; ^{1}H-NMR (DMSO-d_6) δ: 2.18 (s, 3H, $COCH_3$), 4.01 (s, 3H, OCH_3), 5.85 (d, J=1.3 Hz, 1H, C=C$\underline{H}_2$), 7.11 (s, 1H, C=C$\underline{H}_2$), 7.97 (s, 1H, arom. 3-H), 7.99 (s, 1H, arom. 6-H), 9.37 (s, 1H, CHO), 9.65 (br s, 1H, CONH), 10.24 (s, 1H, NHCO). EI-MS *m/z*: 297 (M^+). **35**; An analytical sample was obtained by recrystallization from iso-PrOH–Et_2O, mp 227—227.5 °C (lit.[27] mp 210 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (s, 3H, $COCH_3$), 4.00 (s, 3H, OCH_3), 5.82 (br s, 1H, CON$\underline{H}_2$), 7.68 (br s, 1H, CON$\underline{H}_2$), 7.80 (br s, 1H, CONH), 8.30 (s, 1H, arom. 3-H), 8.47 (s, 1H, arom. 6-H). EI-MS *m/z*: 243 (M^+). IR (KBr) ν cm^{-1}: 3398, 3317, 1682, 1647, 1583, 1425, 1371. *Anal.* Calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; Cl, 14.61; N, 11.54. Found: C, 49.37; H, 4.55; Cl, 14.49; N, 11.47.

***N*-(1,3-Dihydroxy-2-propyl)-1*H*-indazole-3-carboxamide (37)** A mixture of diindazolo[2,3-*a*:2′,3′-*d*]pyrazine-7,14-dione[21] (**36**, 20.0 g, 69 mmol), **21** (19.0 g, 0.21 mol), and DMF (200 ml) was stirred at room temperature for 12 h. The reaction mixture was concentrated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH = 10/1 to give 12.7 g (78%) of **37** as a solid. An analytical sample was obtained by recrystallization from EtOH, mp 128—130 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.37—3.73 (m, 4H, C$\underline{H}_2$OH × 2), 4.00 (m, 1H, 2-CH), 4.86 (t, J=11 Hz, 2H, $CH_2O\underline{H} \times 2$), 7.25 (dd, J=8, 8 Hz, 1H, indazole 5-H), 7.42 (dd, J=8, 8 Hz, 1H, indazole 6-H), 7.62 (d, J=8 Hz, 1H, indazole 7-H), 7.73 (d, J=8 Hz, 1H, CONH), 8.18 (d, J=8 Hz, 1H, indazole 4-H), 13.59 (s, 1H, NH). SI-MS *m/z*: 236 (MH^+). IR (KBr) ν cm^{-1}: 1641, 1620, 1562. *Anal.* Calcd for $C_{11}H_{13}N_3O_3 \cdot 0.25H_2O$: C, 55.11; H, 5.68; N, 17.53. Found: C, 55.16; H, 5.42; N, 17.52.

***N*-(1,3-Dihydroxy-2-propyl)-1-ethoxycarbonyl-1*H*-indazole-3-carboxamide (38)** Ethyl chloroformate (5.3 g, 49 mmol) was added dropwise to a suspension of **37** (11.8 g, 50 mmol), Et_3N (6.0 g, 59 mmol), and $CHCl_3$ (500 ml) at *ca.* 0 °C. The mixture was stirred at room temperature for 12 h and then washed successively with water and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with $CHCl_3$/MeOH = 10/1 to give 9.9 g (64%) of **38** as a solid. An analytical sample was obtained by trituration from Et_2O, mp 120—121 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.48 (t, J=7 Hz, 3H, $CH_2C\underline{H}_3$), 3.45—3.75 (m, 4H, C$\underline{H}_2$OH × 2), 4.05 (m, 1H, 2-CH), 4.58 (q, J=7 Hz, 2H, CH_2CH_3), 4.83 (t, J=5 Hz, 2H, $CH_2O\underline{H} \times 2$), 7.50 (dd, J=8, 8 Hz, 1H, indazole 5-H), 7.70 (dd, J=8, 8 Hz, 1H, indazole 6-H), 8.00 (d, J=8 Hz, 1H, CONH), 8.19 (d, J=8 Hz, 1H, indazole 7-H), 8.29 (d, J=8 Hz, 1H, indazole 4-H). SI-MS *m/z*: 308 (MH^+). IR (KBr) ν cm^{-1}: 1649, 1545. *Anal.* Calcd for $C_{14}H_{17}N_3O_5$: C, 53.16; H, 5.74; N, 13.28. Found: C, 53.28; H, 5.57; N, 13.30.

***N*-(2,2-Dimethyl-1,3-dioxan-5-yl)-1*H*-indazole-3-carboxamide (40)** A mixture of 1*H*-indazole-3-carboxylic acid[22] (**39**, 5.0 g, 31 mmol), CDI (5.5 g, 34 mmol), and DMF (100 ml) was stirred at room temperature for 4 h. After **31** (4.9 g, 37 mmol) was added, the whole was stirred at the same temperature for an additional 12 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% aqueous NaOH solution, water, and brine. The solvent was evaporated to give 7.0 g (82%) of **40** as a solid. An analytical sample was obtained by recrystallization from acetone, mp 170—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.50, 1.54 (each s, each 3H, 2-CH_3), 3.90 (d, J=15 Hz, 2H, 4-C$\underline{H}_2$, 6-C$\underline{H}_2$), 4.14 (m, 1H, 5-CH), 4.25 (d, J=15 Hz, 2H, 4-C$\underline{H}_2$, 6-C$\underline{H}_2$), 7.23—7.52 (m, 3H, indazole 5-H, 6-H, CONH), 7.93 (d, J=8 Hz, 1H, indazole 7-H), 8.36 (d, J=8 Hz, 1H, indazole 4-H), 10.92 (br s, 1H, NH). SI-MS *m/z*: 276 (MH^+). IR (KBr) ν cm^{-1}: 1645, 1530. *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.77; H, 6.16; N, 15.16.

1-Benzyloxycarbonyl-*N*-(1,3-dihydroxy-2-propyl)-1*H*-indazole-3-carboxamide (41) Benzyl chloroformate (49.1 g, 0.29 mol) was added dropwise to a mixture of **40** (72.0 g, 0.26 mol), K_2CO_3 (39.7 g, 0.29 mol), THF (300 ml), and H_2O (300 ml) kept at *ca.* 15 °C. The whole was stirred at room temperature for 3 h, acidified with 35% aqueous HCl, and then stirred at room temperature for an additional 2 h. The reaction mixture was neutralized with 48% aqueous NaOH solution, and THF was evaporated. The resulting precipitates were collected by filtration and washed successively with water and Et_2O to give 90.8 g (94%) of **41**. An analytical sample was obtained by recrystallization from acetone, mp 162—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.42—3.70 (m, 4H, C$\underline{H}_2$OH × 2), 4.04 (m, 1H, 2-CH), 4.82 (t, J=11 Hz, 2H, $CH_2O\underline{H} \times 2$), 5.61 (s, 2H, OCH_2Ph), 7.35—7.75 (m, 7H, indazole 5-H, 6-H, arom. H), 8.02 (br d, J=9 Hz, 1H, CONH), 8.18 (d, J=8 Hz, 1H, indazole 7-H), 8.30 (d, J=8 Hz, 1H, indazole 4-H). SI-MS *m/z*: 370 (MH^+). IR (KBr) ν cm^{-1}: 1747, 1670, 1568. *Anal.* Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.57; H, 5.15; N, 11.34.

***N*-(1,3-Dihydroxy-2-propyl)-1-methoxymethyl-1*H*-indazole-3-carboxamide (42)** Compound **40** (34.8 g, 0.13 mol) was added portionwise to a suspension of potassium *tert*-butoxide (17.0 g, 0.15 mol) in THF (350 ml) at *ca.* 5 °C. The mixture was stirred for 0.5 h at *ca.* 5 °C, and then chloromethyl methyl ether (12.3 g, 0.15 mol) was added dropwise at the same temperature. The whole was stirred at room temperature for 16 h and acidified with 1 N aqueous HCl (180 ml). The reaction mixture was stirred for an additional 2 h at the same temperature and neutralized with 20% aqueous K_2CO_3 solution. The solvent was concentrated and cooled to *ca.* 5 °C. The resulting precipitates were collected by filtration and washed with water to give 33.0 g (93%) of **42**.

An analytical sample was obtained by recrystallization from Et_2O, mp 113—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.2 (br s, 2H), 3.31 (s, 3H, CH_2OCH_3), 3.90—4.18 (m, 4H), 4.22 (m, 1H), 5.70 (s, 2H, CH_2OCH_3), 7.32 (dd, J=8, 8 Hz, 1H, indazole 5-H), 7.47 (dd, J=8, 8 Hz, 1H, indazole 6-H), 7.59 (d, J=8 Hz, 1H, indazole 7-H), 7.70 (d, J=8 Hz, 1H, CONH), 8.36 (d, J=8 Hz, 1H, indazole 4-H). EI-MS m/z: 279 (M^+), 248. IR (KBr) ν cm^{-1}: 1645, 1537. *Anal.* Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 55.69; H, 6.13; N, 14.84.

2-(1-Ethoxycarbonyl-, 1-Benzyloxycarbonyl-, and 1-Methoxymethyl-1*H*-indazole-3-carbonylamino)propenals (43, 45, 46) In a similar manner to that described for **17a**, compounds **43**, **45**, and **46** were prepared from **38**, **41**, and **42**, respectively. The chemical data for these compounds are summarized in Table 1.

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1-methoxymethyl-1*H*-indazole-3-carboxamide (48)** In a similar manner to that described for **24**, **48** was obtained from **46** and **12o** in 78% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H, NCH_3), 2.50—3.12 (m, 8H), 3.50 (s, 3H, CH_2OCH_3), 3.60 (d, J=13 Hz, 1H, CH_2Ph), 3.71 (d, J=13 Hz, 1H, CH_2Ph), 4.39 (m, 1H, 6-CH), 5.75 (s, 2H, CH_2OCH_3), 7.1—7.5 (m, 7H), 7.59 (d, J=8 Hz, 1H, indazole 7-H), 8.02 (d, J=8 Hz, 1H, CONH), 8.38 (d, J=8 Hz, 1H, indazole 4-H). EI-MS m/z: 407 (M^+).

***N*-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide (4)** A) In a similar manner to that described for **24**, **43** and **46** were treated with **12o** to give **4** in 23% and 70% yields, respectively, as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (s, 3H, NCH_3), 2.5—3.0 (m, 8H), 3.62 (d, J=13 Hz, 1H, CH_2Ph), 3.68 (d, J=13 Hz, 1H, CH_2Ph), 4.55 (m, 1H, 6-CH), 7.12—7.45 (m, 8H), 8.42 (d, J=8 Hz, 1H, indazole 4-H), 8.97 (d, J=8 Hz, 1H, CONH), 14.02 (br s, 1H, NH). IR (neat) ν cm^{-1}: 1645, 1531. SI-MS m/z: 364 (MH^+). B) A mixture of **48** (1.0 g, 2.5 mmol) and 10% aqueous HCl (20 ml) was heated to reflux for 0.5 h and then cooled to *ca.* 5 °C. The solution was basified with 10% aqueous NaOH solution and extracted with $CHCl_3$. The extract was washed with brine and concentrated to leave a residue, which was chromatographed on silica gel with $CHCl_3$/MeOH = 50/1 to give 730 mg (82%) of **4**. This compound was identical with the sample obtained above, based on comparisons of TLC behavior and IR and ^{1}H-NMR spectra.

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