SYNTHESIS OF ANGULAR BENZODIPYRAZOLES AND RELATED SYSTEMS

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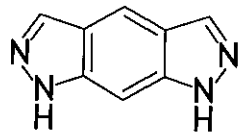
Abstract - A series of benzo[1,2-c:3,4-c′]dipyrazoles was prepared from cyclohexane-1,3-dione. Several related systems with different central rings were also prepared. In addition, benzo[1,2-c:4,3-c′]dipyrazoles were synthesized from 1,4-cyclohexanedione monoethylene ketal.

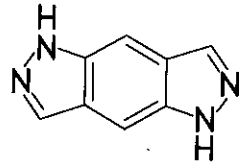
We recently described syntheses of linear benzodipyrazoles, namely, benzo[1,2-c:5,4-c′]dipyrazoles.[1] The parent compound of this ring system is shown below. Since these compounds were found to be adenosine antagonists, and some were more potent than theophylline, we subsequently designed syntheses of related angular benzodipyrazoles. This report describes the preparation of benzo[1,2-c:3,4-c′]dipyrazoles and benzo[1,2-c:4,3-c′]dipyrazoles. Also described are other systems related to the angular systems with modified central rings.

Syntheses of the tetrahydroindazolones required for the preparation of benzo[1,2-c:3,4-c′]dipyrazoles are shown in Scheme I. Treatment of cyclohexane-1,3-dione (1) with sodium acetate and acetic anhydride gave trione (2),[2] which was converted to indazolones (3a)[3] and (3b)[3] with hydrazine and methylhydrazine, respectively. Enamine dione (4), which is accessible from 1 and dimethylformamide dimethyl acetal, gave indazolones (3c) and (3d)[3] when treated with methylhydrazine and benzylhydrazine, respectively.

Benzodipyrazole Systems

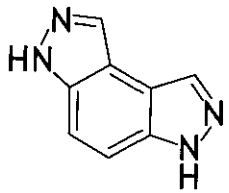


linear

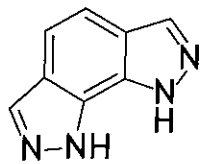


benzo[1,2-c:5,4-c']dipyrazole

benzo[1,2-c:4,5-c']dipyrazole

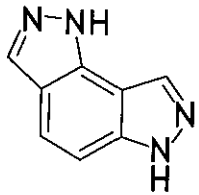


angular

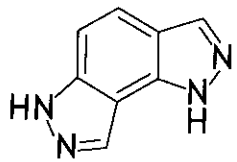


benzo[1,2-c:4,3-c']dipyrazole

benzo[2,1-c:3,4-c']dipyrazole

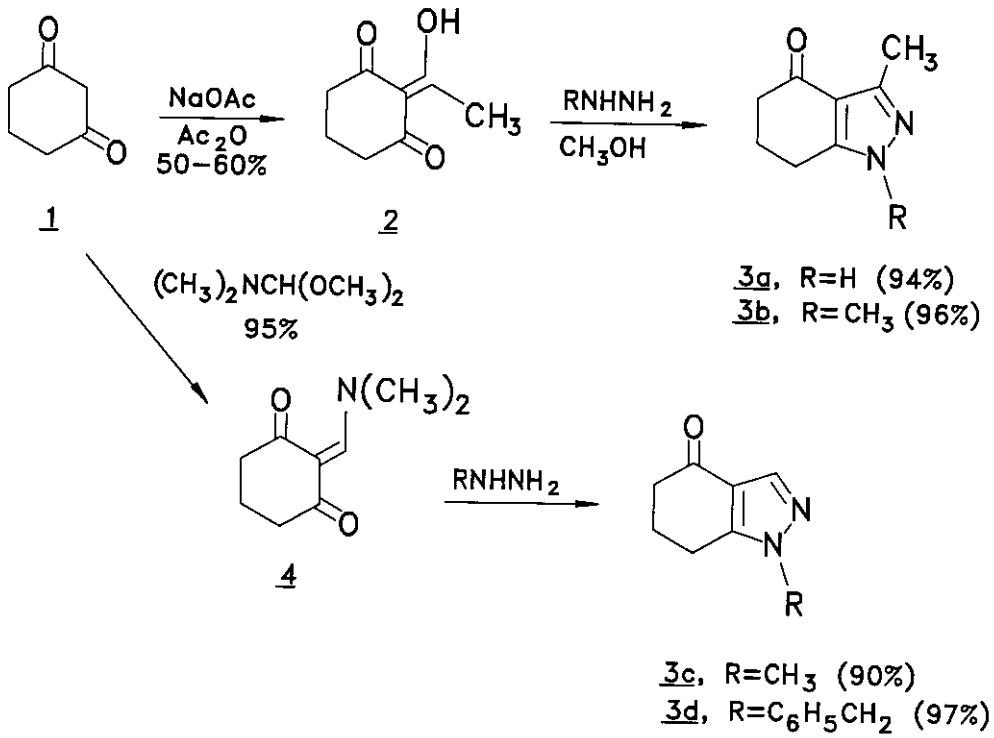


angular degenerate



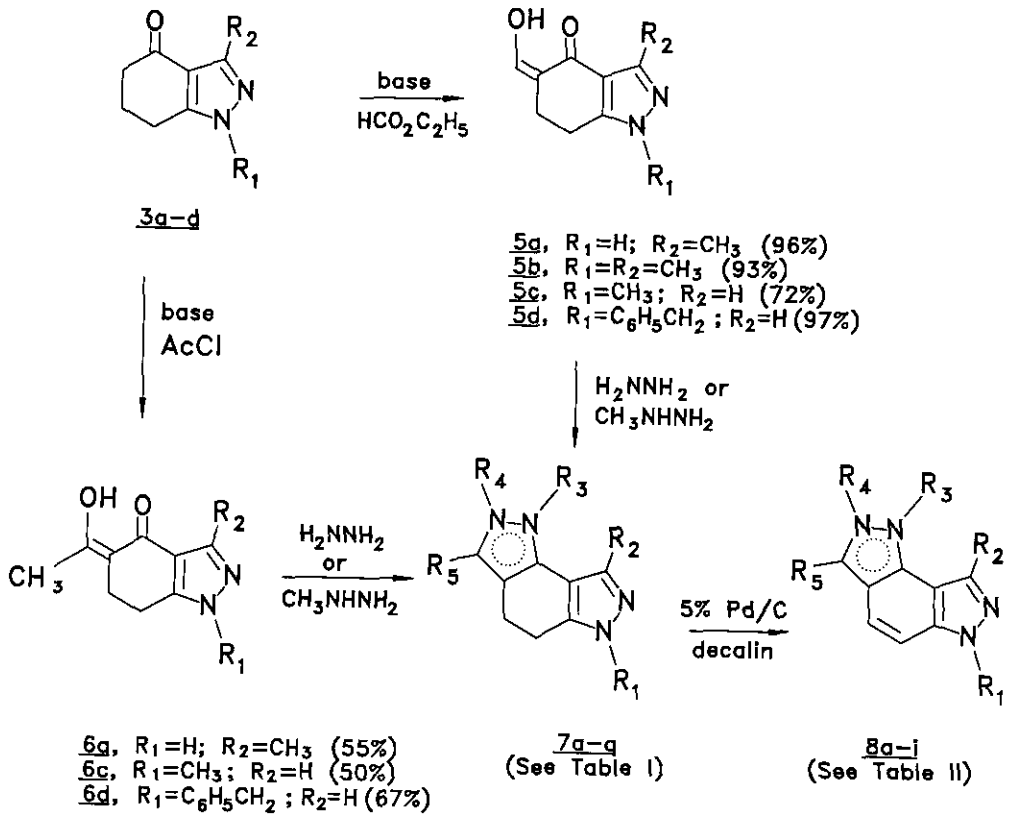
benzo[1,2-c:3,4-c']dipyrazole

Scheme I



Tetrahydroindazolones (3a-d) were converted to the angular dihydrobenzo[1,2-c:4,3-c']dipyrazoles (7a-q) and corresponding fully unsaturated compounds (8a-i) as shown in Scheme II. Treatment of 3b-d with ethyl formate and sodium hydride in either toluene or tetrahydrofuran and a few drops of ethanol gave β-keto aldedydes (5b-d), respectively. To effect the formylation of (3a), the dianion was generated with lithium diisopropylamide (LDA) and treated with ethyl formate at -78°C to give (5a). Acetylation of 3a and 3c was effected by anion generation with LDA followed by treatment with acetyl chloride. Two equivalents of LDA were used with 3c, one of which presumably traps the resulting acidic β-diketone as its lithium enolate. Three equivalents of LDA were required for 3a, an extra equivalent being needed to abstract the acidic NH hydrogen. When 3d was treated with two equivalents of LDA, a complex mixture of products was observed after treatment with acetyl chloride. When two equivalents of lithium bis(trimethylsilyl)amide were employed, however, a 67% yield of 6d was obtained.

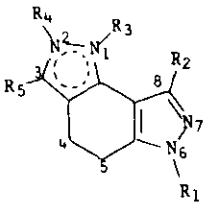
Scheme II



Treatment of β-dicarbonyl compounds (5a-d), (6a), (6c), and (6d) with hydrazine and methylhydrazine gave tetrahydrobenzo[1,2-c:3,4-c′]dipyrazoles (7a-q), or their immediate precursors which are displayed in Table I. Compounds which were produced directly by cyclization of β-dicarbonyl units with hydrazines were prepared by Method A (see Experimental Section for a detailed description of methods). Compounds prepared by Method B are those in which an additional alkyl group was added to the newly formed pyrazole ring by an alkylation step (dimethylformamide, sodium hydride, and the appropriate alkyl iodide). Method C indicates that removal of a benzyl group (sodium in liquid ammonia) was the final step.

Compounds of Table I (7a-q) were treated with 5% Pd/C in decalin to produce the dihydrobenzo[1,2-c:4,3-c′]dipyrazoles (8a-i) which are displayed in Table II.

Table I. 1,4,5,6- and 2,4,5,6-Tetrahydrobenzo[1,2-c:3,4-c']dipyrazoles



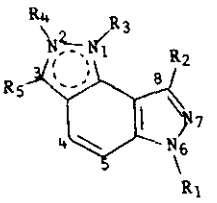
Cpd No.	R_1	R_2	R_3	R_4	R_5	Yield (%)	mp (°C)[a]	Method[b]
7a[c]	CH_3	H	CH_3	–	H	51	222-226 (dec)	A
7b	CH_3	H	H	–	H	80	242-245	A
7c	CH_3	H	–	CH_3	H	33	140-145	B
7d	CH_3	H	H	–	CH_3	81	184-186	A
7e[c]	CH_3	H	CH_3	–	CH_3	20	252-254	B
7f	CH_3	H	–	CH_3	CH_3	29	172-176	B
7g	H	CH_3	H	–	H	64	224-226.5	A
7h	CH_3	CH_3	H	–	H	71	212-213	A
7i	CH_3	CH_3	CH_3	–	H	53	166-167.5	A
7j	H	CH_3	CH_3	–	H	41	174.5-177	A
7k	H	CH_3	H	–	CH_3	94	257-258 (dec)	A
7l	$C_6H_5CH_2$	H	CH_3	–	H	68	94-97.5	A
7m	H	H	CH_3	–	H	78	180-186	C
7n	$C_6H_5CH_2$	H	H	–	H	84	217-219	A
7o	H	H	H	–	H	76	219-221	C
7p	$C_6H_5CH_2$	H	H	–	CH_3	79	182-184	A
7q	H	H	H	–	CH_3	97	250-252	C

[a]Spectral data were consistent with structure (see Experimental Section). Empirical formula was substantiated by combustion analysis or high resolution mass spectrometry.

[b]See Experimental Section for a description of the methods employed.

[c]Isolated as the monohydrochloride salt.

Table II. 1,6- and 2,6-Dihydrobenzo[1,2-c:3,4-c']dipyrazoles

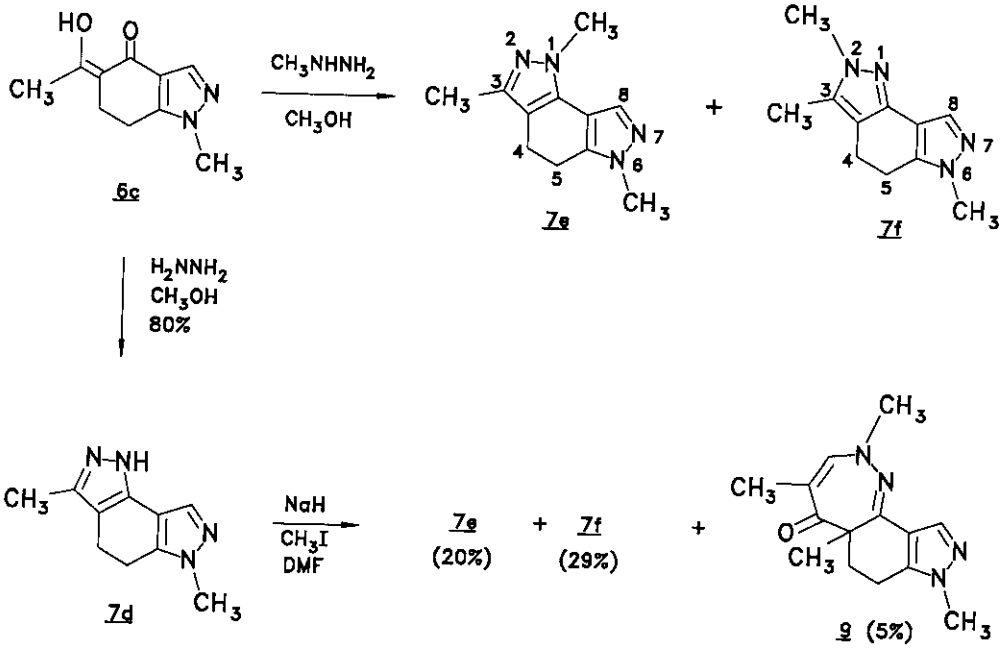


Cpd No.	R_1	R_2	R_3	R_4	R_5	Yield (%)	mp (°C)[a]
8a	CH_3	H	H	–	H	71	180-184.5
8b	CH_3	H	CH_3	–	H	82	119-122
8c	CH_3	H	–	CH_3	H	84	132-135.5
8d	CH_3	H	H	–	CH_3	45	158.5-162
8e	H	CH_3	H	–	CH_3	70	>290
8f	H	CH_3	H	–	H	72	249-251
8g	H	H	H	–	H	68	290 (dec)
8h	CH_3	H	–	CH_3	CH_3	48	128-134
8i	H	H	H	–	CH_3	31	277-279.5

[a]Spectral data were consistent with structure (see Experimental Section). Empirical formula was substantiated by combustion analysis or high resolution mass spectrometry.

Cyclization of 1,3-dicarbonyl compounds with methylhydrazine gave mixtures which were separated either by selective recrystallization techniques or flash chromatography. Structural assignments were made on the basis of ^{1}H nmr chemical shift positions and nuclear Overhauser enhancement (nOe) effects. This is illustrated by the assignment of structures for both 7e and 7f which were produced in approximately equimolar amounts from 6c (Scheme III). Chemical shifts for the N1-CH_3 and N6-CH_3 groups in the ^{1}H nmr (CD_3OD) spectrum of 7e were assigned at δ 4.15 and δ 3.95, respectively, while the N2-CH_3 and N6-CH_3 of 7f were assigned at δ 3.98 and δ 3.93, respectively. The anisotropy of the N6,N7-pyrazole ring causes the N1-CH_3 group of 7e to

Scheme III



appear at significantly lower field than does the N2-CH_3 of 7f. Moreover, when the N1-CH_3 of 7e was irradiated, in an nOe experiment, the C8-H signal at δ 8.15 was enhanced, indicating a proximal relationship. No C8-H signal enhancement at δ 7.90 was observed when the N2-CH_3 signal of 7f was irradiated.

Benzodipyrazoles (7e) and (7f) were also prepared by methylating 7d, which was readily obtained in high yield from diketone (6c) (Scheme III). In addition to monoalkylated products (7e) and (7f) we obtained condensed 1,2-diazepine (9), which arises from trialkylation and the involvement of solvent as a reactant. A proposed mechanism for the formation of 9 is presented in Scheme IV, wherein the major monoalkylated product (7e) is first methylated at C-3a via enamine

activation to give intermediate (10). Subsequent methylation of the exomethylene enamine provides enamine (11), which reacts with dimethylformamide as shown to give zwitterionic intermediate (12). Hydrolysis of 12 after quenching the reaction would give the hydrazone dione (13), which cyclized to 9 via addition of the methylamino nucleophile to the formyl group. Cyclization of intermediate (13) by addition of the methylamino nucleophile to the ketone was ruled out since the product did not contain an aldehyde functionality. ^{1}H nmr, ^{13}C nmr and mass spectral data were consistent with the proposed diazepinone (9), as was the combustion analysis.

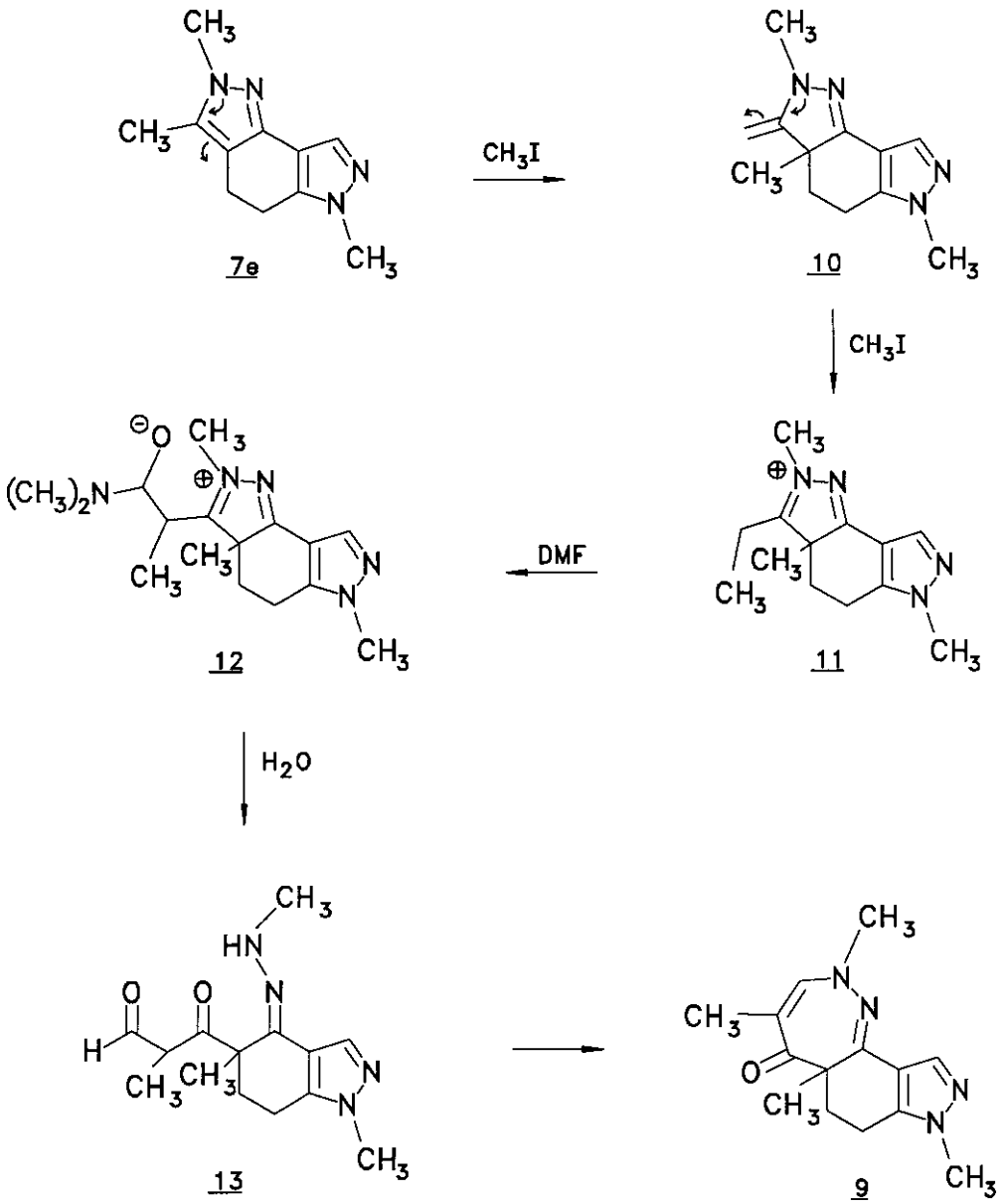
To vary the relative positions of the pyrazole rings to study the effect on receptor interaction, compounds were synthesized in which the central ring of the benzodipyrazoles was smaller and larger by one methylene unit. The syntheses of cyclopenta[1,2-c:3,4-c']dipyrazoles (18) and (19) are shown in Scheme V. Enamine dione (14)[2] was treated with benzylhydrazine to give 15 (53%), the isolable product of a Michael addition-elimination sequence. Cyclization to cyclopentapyrazolone (16) (44%) was effected with p-toluenesulfonic acid in toluene. Formylation of 16 with sodium hydride and ethyl formate gave 17 (86%) which cyclized with hydrazine in methanol to cyclopentadipyrazole (18) in 86% yield. Deprotection of 18 with sodium in liquid ammonia gave 19 in 50% yield.

The synthesis of compounds where the central ring is one methylene unit larger, namely, cyclohepta[1,2-c:3,4-c']dipyrazoles, is shown in Scheme VI. Although cycloheptane-1,3-dione was a potential starting material for this ring system, the known methods of synthesis are tedious and inefficient.[4,5] Since ring expansion reactions using ethyl diazoacetate in the presence of a Lewis acid such as boron trifluoride etherate have been reported,[6,7] it seemed attractive to attempt such a ring expansion with 1,5,6,7-tetrahydro-1-methylindazol-4-one (3c), which is readily available.[2] Although carbon insertion with ethyl diazoacetate normally occurs on the least hindered side of unsymmetrical ketones,[7] the major product which was isolated from 3c and excess ethyl diazoacetate, after insertion, hydrolysis and decarboxylation, was ketone (21), the product arising from insertion on the most hindered side of ketone (3c). Ketone (20), the product arising from insertion on the least hindered side, was also produced, along with cyclooctanone (22), which arose from insertion on both sides of the ketone. Mass balance for the three steps of Scheme VI was a modest 20%, and the ratio of 20:21:22 was approximately 1:2.5:1.

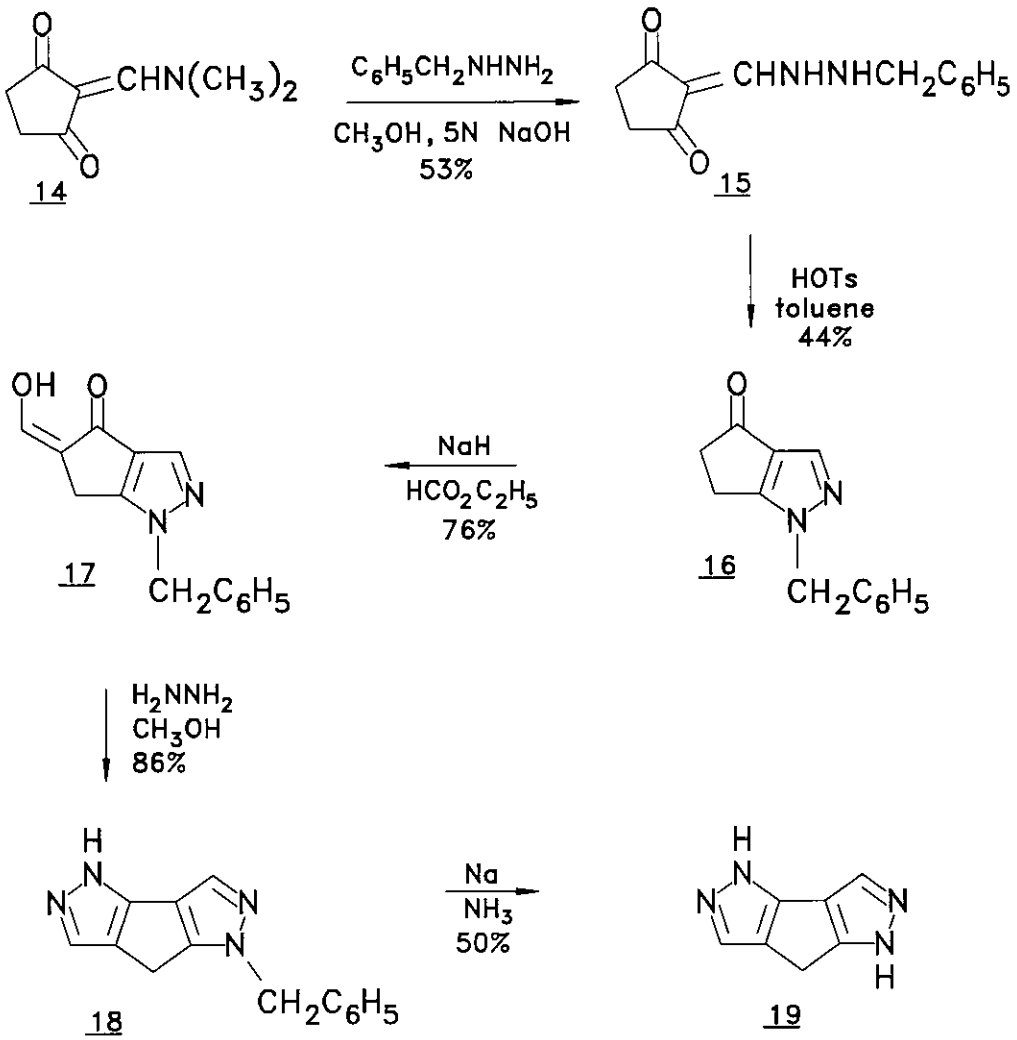
The significant amount of insertion by ethyl diazoacetate at the most hindered side of ketone (3c) suggested pyrazole participation. A proposed mechanistic interpretation of this involvement is shown in Scheme VII, where intermediate (23) is produced from nucleophilic attack

of ethyl diazoacetate at the 4-position of 3c. Pyrazole assistance in the expulsion of nitrogen, as shown, would produce the zwitterionic cyclopropane intermediate (24). Alternatively, 24 could arise from pyrazole (26) by the loss of nitrogen as shown. Pyrazole (26) is the projected product of cycloaddition of 3c and ethyl diazoacetate. Finally, intermediate (24) could undergo ring expansion by rearomatization of the pyrazole.

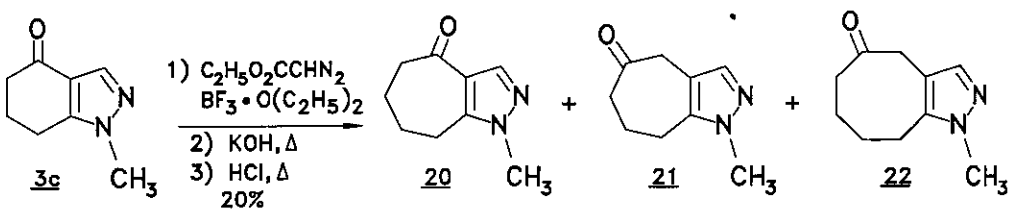
Scheme IV



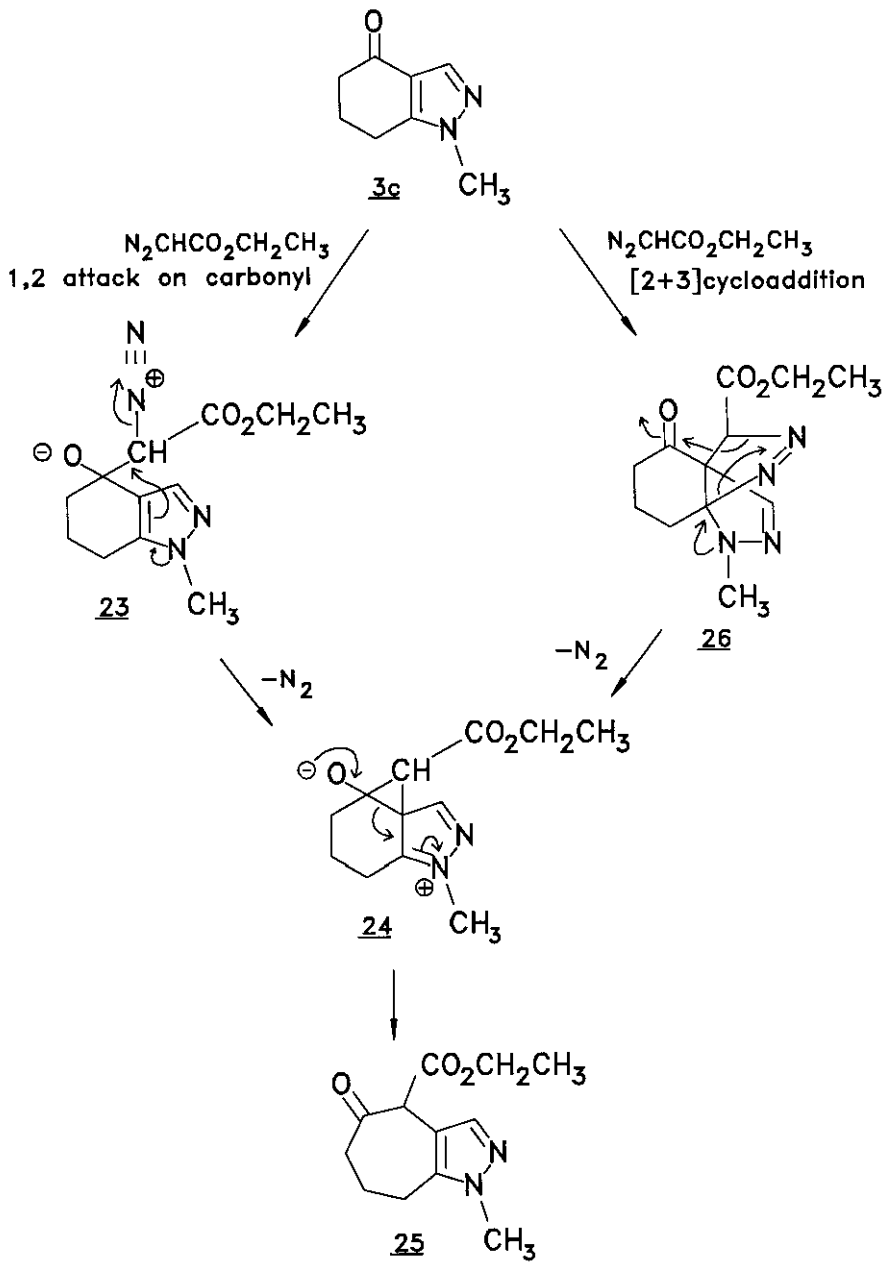
Scheme V



Scheme VI

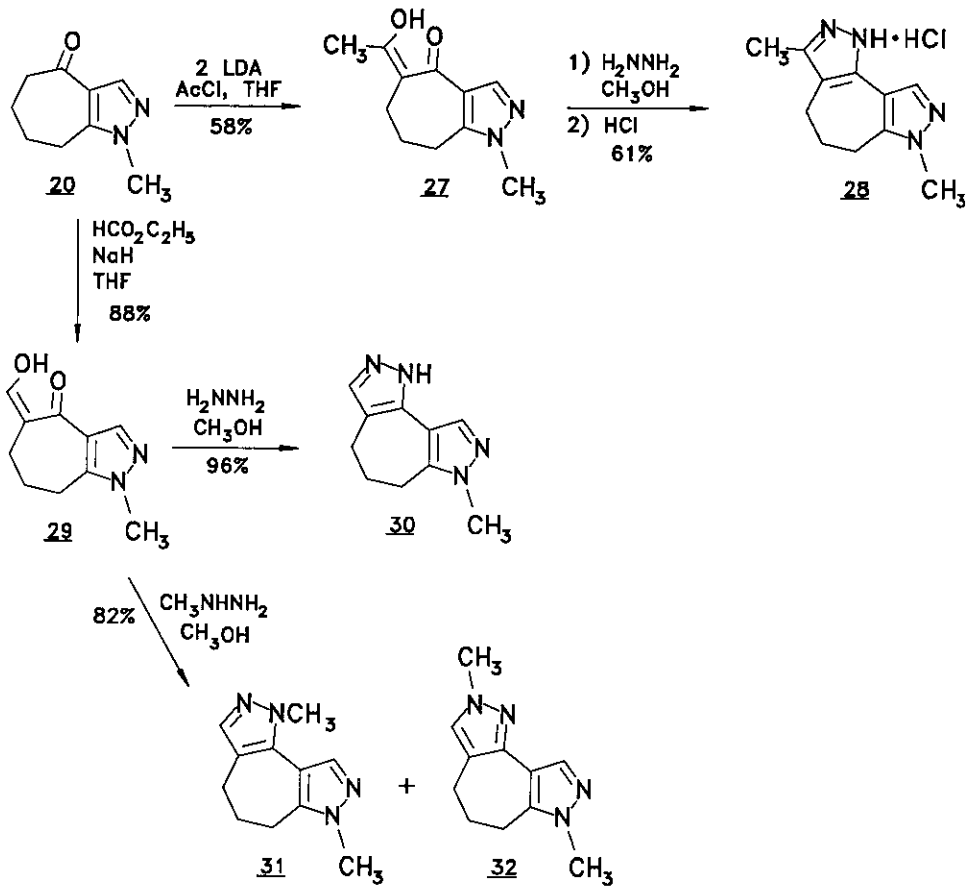


Scheme VII



The preparation of cyclohepta[1,2-c:3,4-c']dipyrazoles from 20 is shown in Scheme VIII. Acetylation of the anion of 20 generated with LDA gave β-diketone (27), which was condensed with hydrazine to produce cycloheptadipyrazole (28). Formylation of 20 with ethyl formate gave β-keto aldehyde (29), which was condensed with hydrazine to give 30 and with methylhydrazine to give the isomeric cycloheptadipyrazoles (31) (28%) and (32) (54%).

Scheme VIII



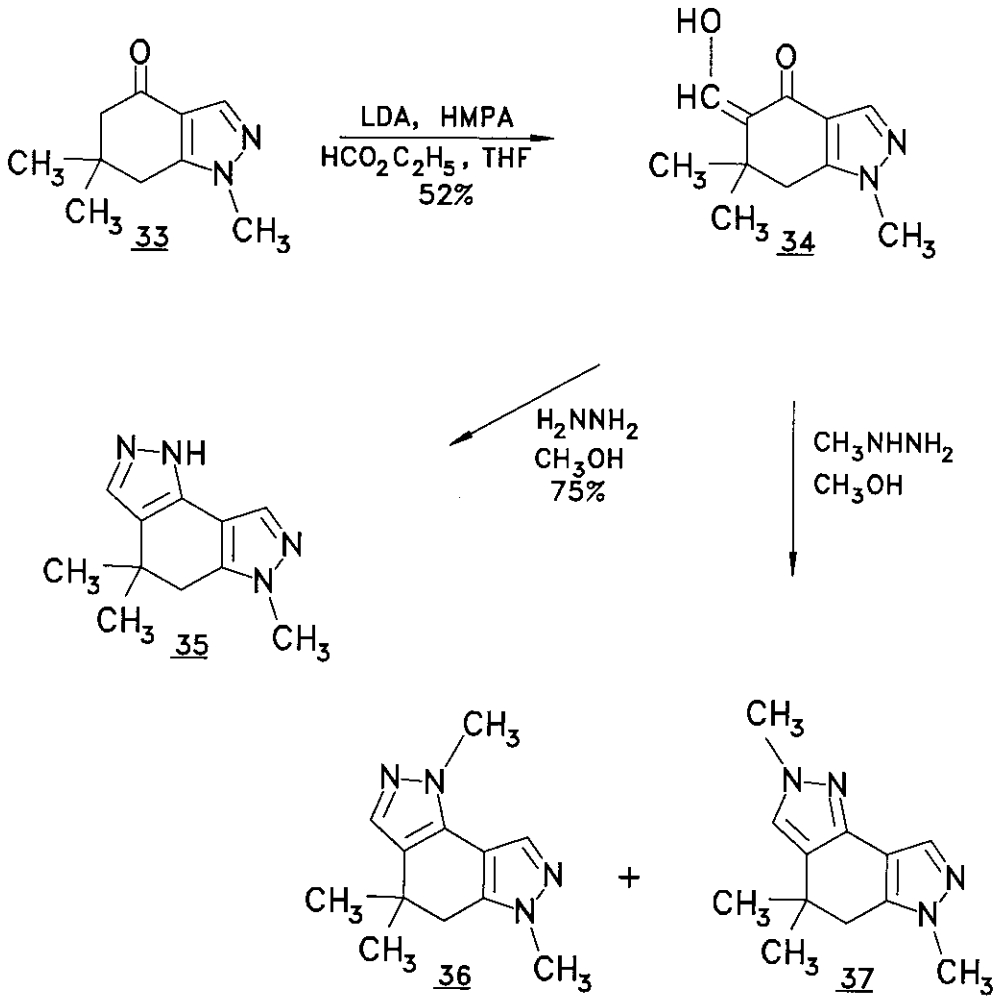
Two sets of fused dipyrazole ring systems were also prepared in which the central six-membered ring could not be metabolically aromatized. Formylation of gem-dimethylindazolone (33),[2] by generation of the anion with LDA in tetrahydrofuran and hexamethylphosphoramide (HMPA) and treatment with ethyl formate gave β-keto aldehyde (34) (52%), which cyclized on treatment with hydrazine to give benzodipyrazole (35) in 75% yield, as shown in Scheme IX. Treatment of 34 with methylhydrazine gave the isomeric benzodipyrazoles (36) (54%) and (37) (43%), which were separated by fractional recrystallization.

The other fused ring system in which the central ring of the fused dipyrazole could not be metabolically oxidized to an aromatic ring was the thiopyrano[3,2-c:5,4-c′]dipyrazole system shown in Scheme X. Formylation of 1,4,5,7-tetrahydro-1-methyl-4-oxothiopyrano[3,4-c′]pyrazole (38) by treatment of the sodium enolate with ethyl formate gave β-keto aldehyde (39) (75%). Treatment of 39 with hydrazine and benzylhydrazine gave thiopyranodipyrazoles (40) (93%) and (43) (69%), respectively. Oxidation of 40 and 43 with one equivalent of m-chloroperoxybenzoic

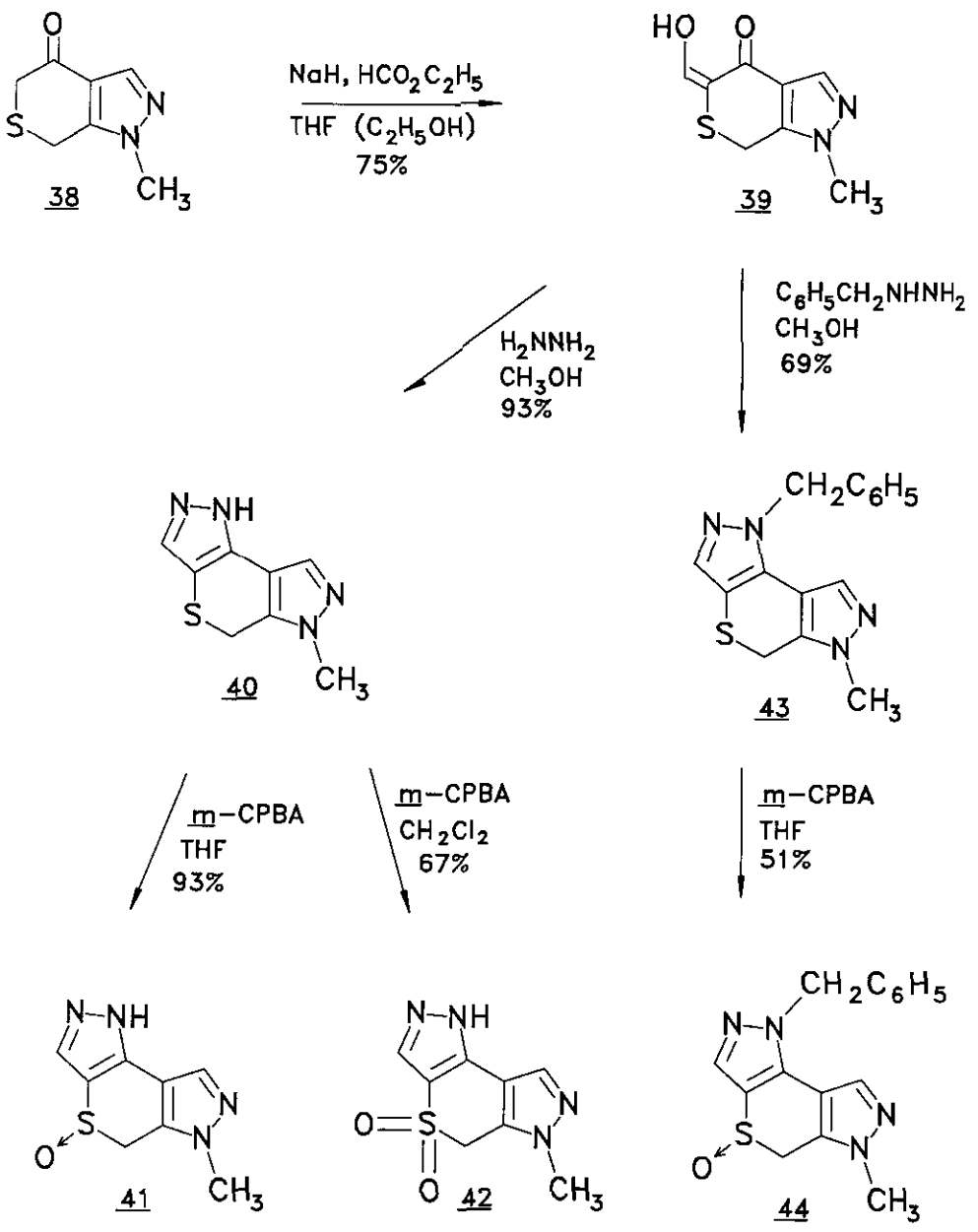
acid (m-CPBA) gave sulfoxides (41) (93%) and (44) (51%), respectively, while oxidation of 40 with two equivalents of m-CPBA gave sulfone (42) (67%). It was recognized that oxidation at sulfur could occur metabolically. The position of the benzyl group on 44 was definitely shown to be at C1 by an nOe study. Irradiation of the benzyl methylene group of 44 produced an nOe effect on C8-H and no nOe effect on C3-H.

Thus, Schemes I-X describe synthetic routes to benzo[1,2-c:3,4-c']dipyrazoles and related angular systems. We had earlier[8] attempted the conversion of readily available 1,5,6,7-tetrahydroindazol-4-ones (Scheme I), using 1,2-carbonyl transposition methodology,[9] to the isomeric 5-ones, which were viewed as starting materials for benzo[1,2-c:4,3-c']dipyrazoles, the angu-

Scheme IX



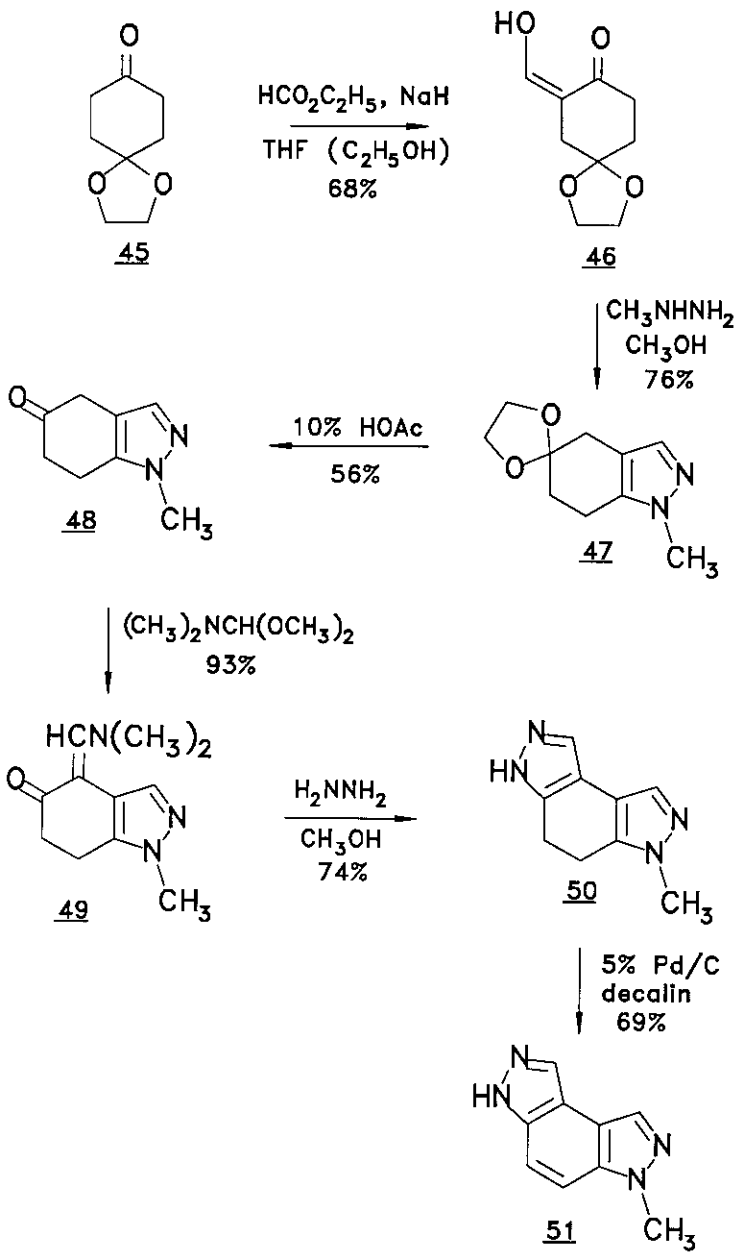
Scheme X



lar "flipped" systems. Since this conversion was unsuccessful, a new route to 1,4,6,7-tetrahydroindazol-5-ones was sought. Treatment of 1,4-cyclohexadione monoethylene ketal (45) with sodium hydride and ethyl formate in tetrahydrofuran containing a drop of ethanol provided the formylated cyclohexanone (46) in 68% yield, as shown in Scheme XI. Dropwise addition of methyl-

hydrazine to a cold solution of 46 in methanol gave the protected indazolone (47) in 76% yield. Interestingly, the regioselectivity of this condensation was lost at higher temperature. Addition of methylhydrazine to 46 in methanol at reflux gave a 1:1 ratio of 47 and its 2-methyl

Scheme XI



isomer. Deprotection of 47 with 10% acetic acid afforded the key intermediate (48), 1,4,6,7-tetrahydro-1-methylindazol-5-one, in 56% yield. Condensation of 48 with N,N-dimethylformamide dimethyl acetal gave enamino ketone (49) (93%) which was treated with hydrazine to afford the "flipped" angular benzodipyrazole, 3,4,5,6-tetrahydro-3-methylbenzo[1,2-c:4,3-c']dipyrazole (50) in 74% yield. Dehydrogenation of 50 with 5% Pd/C in decalin gave the fully unsaturated benzodipyrazole (51) in 69% yield.

In summary, we have described versatile synthetic routes to angular benzo[1,2-c:3,4-c']dipyrazoles and related systems with different central rings, and benzo[1,2-c:4,3-c']dipyrazoles. This methodology should prove useful for the construction of additional tricyclic heterocycles of biological interest.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Flash chromatography was done on silica gel using the solvent system specified. Combustion analyses for C, H and N were performed by Marion Merrell Dow Analytical Laboratories, Cincinnati, Ohio. All new structures are supported with combustion analyses or hrms data, with the exception of indazolones (3d), (5a), (5d), (6a), (6b), and (6d), and cycloheptapyrazolones (20) and (27).

1,5,6,7-Tetrahydro-3-methylindazol-4-one (3a). To an ice cold solution of 33.3 g (0.220 mol) of 2[2] in 400 ml of methanol was added, dropwise, a solution of 7.20 ml (0.220 mol) of hydrazine in 50 ml of methanol. After 20 h at reflux, the solution was concentrated and the residue was triturated with ether to give 31.0 g (94%) of 3a as a yellow, crystalline solid, mp 154-157°C (lit.[10] mp 152-154°C); ^{1}H nmr (DMSO-d_6) δ 13.4-12.7 (br s, 1H, NH), 2.73 (t, J=6 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.66-1.80 (m, 4H, CH_2CH_2).

1,5,6,7-Tetrahydro-1,3-dimethylindazol-4-one (3b). To an ice cold solution of 30.0 g (0.200 mol) of 2[2] in 200 ml of methanol was added, dropwise, a solution of 11.0 ml (0.200 mol) of methylhydrazine in 50 ml of methanol. After heating at reflux for 90 min the solution was concentrated and the residue was triturated with hexane to give 31.6 g (96%) of 3b, mp 82.5-84°C (toluene-hexane) (lit.[3] mp 83-87°C); ^{1}H nmr ($CDCl_3$) δ 3.70 (s, 3H, NCH_3), 2.73 (t, J=6 Hz, 2H, CH_2), 2.40 (s, 3H, CCH_3), 2.60-1.90 (m, 4H, CH_2CH_2).

1,5,6,7-Tetrahydro-1-(phenylmethyl)indazol-4-one (3d). A mixture of 7.80 g (40.0 mmol) of benzylhydrazine dihydrochloride, 100 ml of methanol and 16.0 ml of 5 N sodium hydroxide solution was slowly added to an ice cold solution of 6.70 g (40.0 mmol) of 4[2] in 100 ml of methanol. The reaction mixture was heated at reflux for 90 min, concentrated, and the residue was partitioned between water and methylene chloride. The organic layer was dried ($MgSO_4$) and concentrated to an amber oil which crystallized on standing to give 8.80 g (97%) of 3d, mp 55-59°C; ^{1}H nmr ($CDCl_3$) δ 7.90 (s, 1H, C3-H), 7.45-7.00 (m, 5H, phenyl), 5.27 (s, 2H, benzyl CH_2), 2.73 (t, J=6 Hz, 2H, CH_2), 2.60-1.90 (m, 4H, CH_2CH_2).

1,5,6,7-Tetrahydro-5-hydroxymethylene-3-methylindazol-4-one (5a). To an ice cold solution of 13.9 ml (99.0 mmol) of diisopropylamine in 50 ml of anhydrous tetrahydrofuran was added 38.0 ml (99.0 mmol) of 2.6 M n-butyllithium in hexane. The mixture was cooled to -78°C and a mixture of 4.50 g (30.0 mmol) of 3a in 25 ml of tetrahydrofuran was added dropwise. The mixture was stirred mechanically for 30 min and a solution of 10 ml of ethyl formate in 30 ml of tetrahydrofuran was added dropwise. The mixture was warmed to 0°C and quenched by the addition of water (200 ml). The separated aqueous phase was washed with ether, acidified to pH 4 and extracted with methylene chloride. The combined extracts were dried ($MgSO_4$) and concentrated to leave 5.10 g (96%) of 5a as a yellow semi-solid; ^{1}H nmr ($CDCl_3$) δ 11.60-10.30 (br s, 1H, OH), 7.33 (s, 1H, C=CH), 3.00-2.40 (m, 4H, CH_2CH_2), 2.55 (s, 3H, CH_3).

1,5,6,7-Tetrahydro-5-hydroxymethylene-1,3-dimethylindazol-4-one (5b). A 15.2 g (93.0 mmol) quantity of 3b was combined with 7.44 g (0.186 mol) of sodium hydride (60% suspension in mineral oil), 30 ml of ethyl formate, 2 drops of ethanol and 100 ml of tetrahydrofuran. The mixture was stirred mechanically at reflux for 1 h, cooled, and diluted with water (500 ml) and ether (300 ml). The separated aqueous phase was washed with ether, acidified to pH 4 and extracted with methylene chloride. The combined extracts were dried ($MgSO_4$) and concentrated to leave 16.7 g (93%) of 5b as a brown solid, mp 108-111.5°C (lit.[3] mp 119-122°C); ^{1}H nmr ($CDCl_3$) δ 7.25 (br s, 1H, C=CH), 3.70 (s, 3H, NCH_3), 2.90-2.50 (m, 4H, CH_2CH_2), 2.45 (s, 3H, CCH_3).

1,5,6,7-Tetrahydro-5-hydroxymethylene-1-methylindazol-4-one (5c). A mechanically stirred mixture of 16.8 g (0.110 mol) of 3c,[8] 6.00 g (0.250 mol) of dry sodium hydride, 15 ml of ethyl formate, 3 drops of ethanol and 200 ml of toluene was heated at reflux for 16 h. The mixture was cooled and extracted with water (2 x 200 ml). The aqueous extracts were washed with ether, acidified to pH 4 and extracted with methylene chloride. The extracts were dried ($MgSO_4$) and concentrated and the residue was triturated with ether-hexane to provide 14.6 g (72%) of 5c as a tan solid, mp 93-95°C (lit.[11] mp 101°C); ^{1}H nmr ($CDCl_3$) δ 14.2-13.0 (br s, 1H, OH), 7.80 (s, 1H, C3-H), 7.23 (br s, 1H, C=CH), 3.77 (s, 3H, CH_3), 2.90-2.50 (m, 4H, CH_2CH_2).

1,5,6,7-Tetrahydro-5-hydroxymethylene-1-(phenylmethyl)indazol-4-one (5d). Compound 5d was prepared from 3d using the same method described for the preparation of 5b. Thus, 7.80 g (35.0 mmol) of 3d afforded 8.50 g (97%) of 5d as an amber oil; ^{1}H nmr ($CDCl_3$) δ 7.87 (s, 1H, C3-H), 7.34-6.95 (m, 6H, phenyl and C=CH), 5.25 (s, 2H, benzyl CH_2), 2.70-2.50 (m, 4H, CH_2CH_2).

1,5,6,7-Tetrahydro-5-acetyl-3-methylindazol-4-one (6a). To a solution of 18.5 ml (0.130 mol) of diisopropylamine in 60 ml of anhydrous tetrahydrofuran at 0°C was added 51.0 ml (0.130 mol) of 2.5 M n-butyllithium. The solution was cooled to -78°C and a solution of 6.00 g (40.0 mmol) of 3a in 100 ml of anhydrous tetrahydrofuran was added. After 20 min of mechanical stirring at -78°C, 10 ml of acetyl chloride in 30 ml of anhydrous tetrahydrofuran was added dropwise. The mixture was allowed to warm to ~15°C and quenched by the dropwise addition of water (120 ml). After vigorous stirring, the mixture was diluted with water (800 ml) and the separated aqueous layer was extracted with methylene chloride. The aqueous phase was acidified to pH 4 with concentrated hydrochloric acid and extracted with methylene chloride. The combined extracts were dried ($MgSO_4$) and concentrated to leave crude 6a as an amber oil which was purified by flash chromatography on silica gel (9% 2-propanol in methylene chloride) to afford 3.20 g (55%) of 6a as an oily solid; ^{1}H nmr ($CDCl_3$)[12] δ 10.60-10.00 (br s, 1.5H, NH and OH), 3.55 (t, J=6 Hz, ca 0.5H, O=CCHC=O), 3.00-2.55 (m, 4H, CH_2CH_2), 2.50 (2s, 3H, C3-CH_3), 2.30 (s, ca 1.5H, CH_3CO), 2.10 [s, ca 1.5H, $CH_3C(OH)$=C].

1,5,6,7-Tetrahydro-5-acetyl-1-methylindazol-4-one (6c). Compound 6c was prepared from 3c using the same method described for the preparation of 6a. Thus, 47.2 g (0.320 mol) of 3c gave 30.0 g (50%) of 6c of a yellow oil which crystallized on standing, mp 66-72°C; ^{1}H nmr ($CDCl_3$)[12] δ 7.90 (s, 1H, aromatic), 3.90 (s, 3H, NCH_3), 3.66 (t, J=6 Hz, ca 0.7H, O=CCHC=O), 3.10-2.20 (m, 4H, CH_2CH_2), 2.33 (s, 2H, CH_3CO), 2.20 [s, 1H, $CH_3C(OH)$=C].

1,5,6,7-Tetrahydro-5-acetyl-1-(phenylmethyl)indazol-4-one (6d). To a solution of 321 ml (0.321 mol) of 1.0M lithium bis(trimethylsilyl)amide in 350 ml of anhydrous tetrahydrofuran at -78°C was added, dropwise, a solution of 33.0 g (0.146 mol) of 3d in 150 ml of anhydrous tetrahydrofuran. The reaction mixture was stirred at -78°C for 10 min and treated with a solution of 11.4 g (0.160 mol) of acetyl chloride in 120 ml of anhydrous tetrahydrofuran. Work-up as for 6a gave 26.1 g (67%) of 6d as a yellow oil; ^{1}H nmr ($CDCl_3$)[12] δ 7.85 (s, 1H, C3-H, 7.40-7.00 (m, 5H, aromatic), 5.20 (s, 2H, benzyl CH_2), 3.50 (t, J=6 Hz, ca 0.7H, O=CCHC=O), 3.00-2.00 (m, 4H, CH_2CH_2), 2.25 (s, 2H, CH_3CO), 2.05 [s, 1H, $CH_3C(OH)$=C].

Synthesis of Tetrahydrobenzo[1,2-c:3,4-c']dipyrazoles 7a to 7q. Method A. To a solution of 1,3-dicarbonyl compound (5) or (6) in methanol (40-50 ml/g) at 0°C was added, dropwise, a

solution of an equimolar amount of hydrazine (95%) or methylhydrazine (98%) in methanol (10 ml/g). The solution was heated at reflux until the reaction was complete by tlc (30 min to 4 h). Solvent was removed at reduced pressure and the residue was purified by the method indicated for each compound. **Method B.** A solution of the indicated dipyrazole (7) in dimethylformamide (5 ml/g) was added dropwise to a suspension of sodium hydride (1.1 equivalents) in dimethylformamide (5 ml/g) at 0°C. The mixture was mechanically stirred at 0°C for 30 min, and to it was added, dropwise, a solution of methyl iodide (1.1 equivalents) in dimethylformamide (3 ml/g). The mixture was stirred at room temperature for 2 h, solvent was removed under reduced pressure, and the residue was purified by the method indicated for each compound. **Method C.** The indicated pyrazole (7) was dissolved or suspended in liquid ammonia (50-100 ml/g) and sodium metal was added in small pieces until a blue or blue-green color persisted. The mixture was mechanically stirred for 20 min and ammonium chloride (2.5-5 g/g of 7) was added. The ammonia was allowed to evaporate and the residue was purified by the method indicated for each compound.

1,4,5,6-Tetrahydro-1,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole Monohydrochloride (7a). A 10.5 g (0.059 mol) quantity of 5c was treated with methylhydrazine (Method A). The residue was triturated with ether-ethanol to give 7.30 g (66%) of the benzodipyrazole. This solid was dissolved in 1:3::ethanol:ether and the solution was treated with excess ethereal hydrogen chloride. The resulting yellow solid was collected and recrystallized from 2-propanol-ether to give 6.70 g (51%) of the monohydrochloride salt of 7a as a yellow, crystalline solid, mp 222-226°C (dec); ^{1}H nmr (DMSO-d_6 and D_2O) δ 7.93 (s, 1H, aromatic), 7.87 (s, 1H, aromatic), 4.07 (s, 3H, NCH_3), 3.87 (s, 3H, NCH_3), 3.00 (s, 4H, CH_2CH_2); ms (EI) m/z 188 (molecular ion); Anal. Calcd for $C_{10}H_{12}N_4 \cdot HCl$: C, 53.45; H, 5.83; N, 24.94. Found: C, 53.20; H, 5.83; N, 25.08.

1,4,5,6-Tetrahydro-6-methylbenzo[1,2-c:3,4-c']dipyrazole (7b). A 16.4 g (0.092 mol) quantity of 5c was treated with hydrazine (Method A). The residue was triturated with ether to give 12.8 g (80%) of 7b as a tan, crystalline solid, mp 242-245°C (2-propanol); ^{1}H nmr (DMSO-d_6) δ 7.43 (s, 1H, aromatic), 7.33 (s, 1H, aromatic), 3.70 (s, 3H, NCH_3), 2.80 (s, 4H, CH_2CH_2); ms (EI) m/z 174 (molecular ion); Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 61.88; H, 6.08; N, 32.03.

2,4,5,6-Tetrahydro-2,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole (7c). A 24.3 g (0.140 mol) quantity of 7b was methylated (Method B). The residue was partitioned between water and methylene chloride and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (5% 2-propanol in methylene chloride) to afford 10.4 g (40%) of 7a (free base) and 8.80 g (33%) of 7c as a yellow oil which crystallized on standing, mp 140-145°C; ^{1}H

nmr ($CDCl_3$) δ 7.43 (s, 1H, aromatic), 7.30 (s, 1H, aromatic), 3.73 (s, 6H, both NCH_3), 2.77 (s, 4H, CH_2CH_2); ms (CI) (m/z) 189 (M^++1); Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.49; H, 6.44; N, 29.71.

1,4,5,6-Tetrahydro-3,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole (7d). A 2.50 g (0.013 mol) quantity of 6c was treated with hydrazine (Method A). The residue was triturated with ethanol-ether to give 2.00 g (81%) of 7d as a yellow solid, mp 184-186°C (toluene); ^1H nmr (DMSO-d_6) δ 7.37 (s, 1H, C8-H), 3.67 (s, 3H, NCH_3), 2.80-2.50 (m, 4H, CH_2CH_2), 2.15 (s, 3H, CCH_3); ms (EI) m/z 188 (molecular ion); Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.61; H, 6.52; N, 29.82.

1,4,5,6-Tetrahydro-1,3,6-trimethylbenzo[1,2-c:3,4-c']dipyrazole (7e), 2,4,5,6-tetrahydro-2,3,6-trimethylbenzo[1,2-c:3,4-c']dipyrazole (7f) and 4,5,5a,9-Tetrahydro-3,5a,7,9-tetramethylpyrazolo[3,4-i][1,2]benzodiazepin-6(3H)-one (9). A 14.5-g (0.077 mol) quantity of 6c was treated with methyl iodide (Method B). The residue was partitioned between water and methylene chloride and the organic layer was dried ($MgSO_4$), concentrated and flash chromatographed (7.5:92.5::2-propanol:methylene chloride) to give 4.50 g (29%) of 7f as a colorless, crystalline solid, mp 172-176°C; ^1H nmr ($CDCl_3$) δ 7.60 (s, 1H, C8-H), 3.77 (s, 3H, NCH_3), 3.70 (s, 3H, NCH_3), 2.85-2.60 (m, 4H, CH_2CH_2), 2.20 (s, 3H, CCH_3); ms (EI) m/z 202 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.97; N, 27.70. Found: C, 65.13; H, 6.99, N, 28.10.

Also obtained from the flash chromatography was an inseparable mixture of 7e and 9 (6.50 g) as an oil, which was dissolved in ether and treated with ethereal hydrogen chloride. Recrystallization (2-butanol) of the resulting precipitate provided 3.20 g (20%) of the monohydrochloride salt of 7e as light yellow granules, mp 252-254°C; ^1H nmr (D_2O) δ 7.87 (s, 1H, C8-H), 4.00 (s, 3H, NCH_3), 3.83 (s, 3H, NCH_3), 3.00-2.60 (m, 4H, CH_2CH_2), 2.33 (s, 3H, CCH_3); ms (EI) m/z 202 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_4 \cdot HCl$: C, 55.34; H, 6.33; N, 23.47. Found: C, 55.37; H, 6.46; N, 23.29.

The mother liquor from the recrystallization of 7e was concentrated and partitioned between methylene chloride and aqueous sodium carbonate solution. The organic extract was dried ($MgSO_4$) and concentrated and the resulting amber oil was combined with 20 ml of decalin and 1.5 g of 5% Pd/C and the mixture was heated at 195°C under nitrogen for 2 h to oxidize the remaining amount of 7e. The mixture was cooled, the solvent was removed under reduced pressure and the residue was flash chromatographed (7.5:92.5::2-propanol:methylene chloride) to provide 1.20 g (5%) of 9 as a yellow oil which crystallized on standing, mp 118-126°C; mp 132-133°C (toluene-hexane); ir

(Nujol) 1660 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 7.80 (s, 1H, C1-H), 5.75 (s, 1H, C8-H), 3.70 (s, 3H, NCH_3), 3.66 (s, 3H, NCH_3), 3.20-2.50 (m, 4H, CH_2CH_2), 2.10 (s, 3H, CH_3), 1.50 (s, 3H, CH_3); ^{13}C nmr ($CDCl_3$) δ 194.4 (C6), 151.7 (C10a), 148.9 (C7), 138.8 (C3a), 147.9 (C1), 118.3 (C10b), 103.4 (C8), 46.6 (C5a), 35.9, 35.7 and 35.3 (both NCH_3 and C7-CH_3), 24.9 (C4), 19.1 (C5), 11.1 (C5a-CH_3); ms (EI) m/z 258 (molecular ion); Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.07; H, 7.05; N, 21.55.

1,4,5,6-Tetrahydro-8-methylbenzo[1,2-c:3,4-c']dipyrazole (7g). A 4.90 g (0.028 mol) quantity of 5a was treated with hydrazine (Method A). The residue was purified by flash chromatography (1:9::methanol:methylene chloride) to give 3.10 g (64%) of 7g as a yellow oil which crystallized on standing, mp 224-226.5°C; ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 12.00-9.50 (br s, 2H, both NH), 7.30 (s, 1H, C3-H), 2.80 (s, 4H, CH_2CH_2), 2.45 (s, 3H, CH_3); ms (EI) m/z 174 (molecular ion); Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 61.75; H, 5.99; N, 32.34.

1,4,5,6-Tetrahydro-6,8-dimethylbenzo[1,2-c:3,4-c']dipyrazole (7h). A 4.90 g (0.028 mol) quantity of 5b was treated with hydrazine (Method A). The residue was diluted with ether and cooled and the resulting precipitate was recrystallized (ethanol-water) to give 4.80 g (71%) of 7h as a tan solid, mp 212-213°C; ^1H nmr ($CDCl_3$) δ 11.40-10.70 (br s, 1H, NH), 7.27 (s, 1H, C3-H), 3.66 (s, 3H, NCH_3), 2.75 (m, 4H, CH_2CH_2), 2.45 (s, 3H, CCH_3); ms (EI) m/z 188 (molecular ion); Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.50; H, 6.50; N, 29.79.

1,4,5,6-Tetrahydro-1,6,8-trimethylbenzo[1,2-c:3,4-c']dipyrazole (7i). An 8.80 g (0.046 mol) quantity of 5b was treated with methylhydrazine (Method A). The residue was triturated with ether and the resulting solid was recrystallized (toluene) to give 4.90 g (53%) of 7i as a tan, crystalline solid, mp 166-167.5°C; ^1H nmr ($CDCl_3$) δ 7.23 (s, 1H, C3-H), 4.00 (s, 3H, N1-CH_3), 2.70 (s, 3H, N6-CH_3), 2.67 (s, 4H, CH_2CH_2), 2.45 (s, 3H, CCH_3); ms (EI) m/z 202 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.97; N, 27.70. Found: C, 65.17; H, 7.02; N, 27.39.

1,4,5,6-Tetrahydro-1,8-dimethylbenzo[1,2-c:3,4-c']dipyrazole (7j). A 10.0 g (0.056 mol) quantity of 5a was treated with methylhydrazine (Method A). The residue was triturated with ether and the resulting solid was recrystallized (toluene) to give 4.28 g (41%) of 7j as a cream-colored solid, mp 174.5-177°C; ^1H nmr ($CDCl_3$) δ 7.27 (s, 1H, C3-H), 4.07 (s, 3H, NCH_3), 2.80-2.67 (m, 4H, CH_2CH_2), 2.57 (s, 3H, CCH_3); hrms Calcd for $C_{10}H_{12}N_4$: 188.1062. Found: 188.1057.

1,4,5,6-Tetrahydro-3,8-dimethylbenzo[1,2-c:3,4-c']dipyrazole (7k). A 3.20 g (0.017 mol) quantity of 6a was treated with hydrazine (Method A). The residue was triturated with ether to give 3.00 g (94%) of 7k as a yellow, crystalline solid, mp 257-258°C (dec.)(ethanol-water); ^1H nmr

($CDCl_3$ and DMSO-d_6) δ 6.95 (br s, 2H, both NH), 2.80-2.50 (m, 4H, CH_2CH_2), 2.33 (s, 3H, C8-CH_3), 2.20 (s, 3H, C3-CH_3); ms (EI) m/z 188 (molecular ion); hrms Calcd for $C_{10}H_{12}N_4$: 188.1062. Found: 188.1073.

1,4,5,6-Tetrahydro-1-methyl-6-(phenylmethyl)benzo[1,2-c:3,4-c']dipyrazole (71). A 7.60 g (0.030 mol) quantity of 5d was treated with methylhydrazine (Method A). The residue was purified by flash chromatography (1:4::acetone:methylene chloride) to give 5.40 g (68%) of 71 as a yellow oil which crystallized on standing, mp 94-97.5°C; ^1H nmr ($CDCl_3$) δ 7.56 (s, 1H, C8-H), 7.40-7.00 (m, 6H, C3-H and phenyl), 5.23 (s, 2H, benzyl CH_2), 3.93 (s, 3H, NCH_3), 2.73 (s, 4H, CH_2CH_2); ms (CI) m/z 265 (M^++1); Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.40; H, 6.16; N, 21.03.

1,4,5,6-Tetrahydro-1-methylbenzo[1,2-c:3,4-c']dipyrazole (7m). A 6.20 g (0.023 mol) quantity of 71 was treated with sodium in ammonia (Method C). The residue was partitioned between water and methylene chloride and the organic phase was dried ($MgSO_4$) and concentrated. The residue was triturated with ether to give 3.20 g (78%) of 7m as a white solid, mp 180-186°C (toluene); ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 13.20-12.60 (br s, 1H, NH), 7.66 (s, 1H, C8-H), 7.20 (s, 1H, C3-H), 3.93 (s, 3H, NCH_3), 2.80 (m, 4H, CH_2CH_2); ms (EI) m/z 174 (molecular ion); Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 62.08; H, 5.89; N, 32.21.

1,4,5,6-Tetrahydro-6-(phenylmethyl)benzo[1,2-c:3,4-c']dipyrazole (7n). An 11.0 g (0.043 mol) quantity of 5d was treated with hydrazine (Method A). The residue was triturated with ether to give 9.10 g (84%) of 7n as a yellow crystalline solid, mp 217-219°C (ethanol-water); ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 12.50-11.70 (br s, 1H, NH), 7.60 (s, 1H, C8-H), 7.34-6.90 (m, 6H, C3-H and phenyl), 5.27 (s, 2H, benzyl CH_2), 2.77 (s, 4H, CH_2CH_2); ms (CI) 251 (M^++1); Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.39. Found: C, 71.74; H, 5.82; N, 22.43.

1,4,5,6-Tetrahydrobenzo[1,2-c:3,4-c']dipyrazole (7o). A 5.80-g (0.023 mol) quantity of 7n was treated with sodium in ammonia (Method C). The residue was slurried with water and collected to give 2.80 g (76%) of 7o as a white solid, mp 219-221°C (water); ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 13.00-12.30 (br s, 2H, both NH), 7.60 (s, 1H, aromatic), 7.33 (s, 1H, aromatic), 2.83 (s, 4H, CH_2CH_2); ms (CI) 161 (M^++1); Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.87; H, 5.09; N, 34.93.

1,4,5,6-Tetrahydro-3-methyl-6-(phenylmethyl)benzo[1,2-c:3,4-c']dipyrazole (7p). A 6.10 g (0.023 mol) quantity of 6d was treated with hydrazine (Method A). The residue was triturated

with ether to give 4.80 g (79%) of 7p as a tan, crystalline solid, mp 182-184°C (toluene); ^{1}H nmr ($CDCl_3$) δ 10.80-10.10 (br s, 1H, NH), 7.70 (s, 1H, C8-H), 7.35-6.90 (m, 5H, phenyl), 5.30 (s, 2H, benzyl CH_2), 2.68 (s, 4H, CH_2CH_2), 2.20 (s, 3H, CCH_3); ms (CI) 265 (M^++1); Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.98; H, 6.21; N, 20.94.

1,4,5,6-Tetrahydro-3-methylbenzo[1,2-c:3,4-c']dipyrazole (7q). A 20.0 g (0.076 mol) quantity of 7p was treated with sodium in ammonia (Method C). The residue was slurried with water and the solid was collected to give 12.8 g (97%) of 7q as tan crystals, mp 250-252°C (ethanol-water); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 13.00-11.50 (br s, 2H, both NH), 7.63 (s, 1H, C8-H), 2.90-2.66 (m, 4H, CH_2CH_2), 2.20 (s, 3H, CCH_3); ms 174 (EI) m/z (molecular ion); Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.15. Found: C, 61.66; H, 5.85; N, 31.91.

General Procedure for the Preparation of Dihydrobenzodipyrazoles. The tetrahydrobenzodipyrazole (7) was dissolved or suspended in decalin (10-20 ml per g of 7), 5% Pd/C (0.5-1.0 g per g of 7) was added and the mixture was heated at 195±5°C under nitrogen until reaction was complete by tlc (2.5-48 h). The mixture was filtered and the precipitate was washed with hexane. The precipitate was then stirred with methanol for 30 min and filtered through celite. The filtrate was concentrated and the residue was purified by the method indicated for each compound.

1,6-Dihydro-6-methylbenzo[1,2-c:3,4-c']dipyrazole (8a). The residue obtained by treatment of 4.00 g (0.023 mol) of 7b with Pd/C for 18 h was triturated with 1:1::hexane:ether to give 2.80 g (71%) of 8a as a cream-colored crystalline solid, mp 180-184.5°C (toluene); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 8.10 (s, 1H, C3-H), 7.95 (s, 1H, C8-H), 7.55 (d, J=8 Hz, 1H, C5-H), 7.15 (d, J=10 Hz, 1H, C4-H), 4.05 (s, 3H, NCH_3); ms (CI) m/z 172 (molecular ion); Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.74; H, 4.83; N, 32.27.

1,6-Dihydro-1,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole (8b). The residue obtained from treatment of 6.00 g (0.032 mol) of 7a with Pd/C for 18 h was triturated with hexane to give 4.90 g (82%) of 8b as colorless needles, mp 119-122°C (toluene-hexane); ^{1}H nmr ($CDCl_3$) δ 8.10 (s, 1H, C3-H), 7.90 (s, 1H, C8-H), 7.50 (d, J=8 Hz, 1H, C5-H), 7.05 (d, J=10 Hz, 1H, C4-H), 4.25 (s, 3H, NCH_3), 4.05 (s, 3H, NCH_3); ms (EI) m/z 186 (molecular ion); Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.70; H, 5.35; N, 30.01.

2,6-Dihydro-2,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole (8c). The residue obtained from treatment of 6.00 g (0.032 mol) of 7c with Pd/C for 2.5 h was triturated with hexane to give 5.00 g (84%) of 8c as cream-colored platelets, mp 135-138°C (toluene-hexane); ^{1}H nmr ($CDCl_3$) δ 8.20 (s,

1H, C3-H), 7.73 (s, 1H, C8-H), 7.40 (d, J=8 Hz, 1H, C5-H), 6.95 (d, J=10 Hz, 1H, C4-H), 4.10 (s, 3H, NCH_3), 4.03 (s, 3H, NCH_3); ms (EI) m/z 186 (molecular ion); Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50, H, 5.41; N, 30.09. Found: C, 64.42; H, 5.46; N, 30.28.

1,6-Dihydro-3,6-dimethylbenzo[1,2-c:3,4-c']dipyrazole (8d). The residue obtained from treatment of 3.60 g (0.019 mol) of 7d with Pd/C for 48 h was triturated with ether-hexane to give 1.60 g (45%) of 8d as a cream-colored oil which crystallized on standing, mp 158.5-162°C; ^1H nmr (DMSO-d_6) δ 8.07 (s, 1H, C8-H), 7.60 (d, J=8 Hz, 1H, C5-H), 7.23 (d, J=10 Hz, 1H, C4-H), 4.05 (s, 3H, NCH_3), 2.50 (s, 3H, CCH_3); ms (EI) m/z 186 (molecular ion); Anal. Calcd for $C_{10}H_{10}N_4 \cdot HCl$: C, 53.93; H, 4.98; N, 25.16. Found: C, 53.83; H, 5.18; N, 25.29.

1,6-Dihydro-3,8-dimethylbenzo[1,2-c:3,4-c']dipyrazole (8e). The residue obtained from treatment of 4.70 g (0.036 mol) of 7k with Pd/C for 18 h was triturated with warm methanol and cooled to give 4.70 g (70%) of 8e as a lavender powder, mp > 290°C; ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 13.40-12.80 (br s, 2H, both NH), 7.40 (d, J=8 Hz, 1H, C5-H), 7.10 (d, J=10 Hz, 1H, C4-H), 2.70 (s, 3H, C8-CH_3), 2.50 (s, 3H, C3-CH_3); ms (EI) m/z 186 (molecular ion); Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50, H, 5.41; N, 30.09. Found: C, 64.35; H, 5.53; N, 29.92.

1,6-Dihydro-8-methylbenzo[1,2-c:3,4-c']dipyrazole (8f). The residue obtained from treatment of 3.80 g (0.022 mol) of 7g with Pd/C was treated with hot methanol, filtered and cooled to give 2.7 g (72%) of 8f as a white solid, mp 249-251°C (methanol); ^1H nmr (DMSO-d_6) δ 8.00 (s, 1H, C3-H), 7.50 (d, J=8 Hz, 1H, C5-H), 7.10 (d, J=10 Hz, 1H, C4-H), 2.68 (s, 3H, CH_3); ms (EI) m/z 174 (molecular ion); hrms Calcd for $C_9H_8N_4$: 172.0749. Found: 172.0743.

1,6-Dihydrobenzo[1,2-c:3,4-c']dipyrazole (8g). The residue obtained from treatment of 11.9 g (0.074 mol) of 7o with Pd/C for 18 h was collected to give 8.00 g (68%) of 8g as a cream-colored crystalline solid, mp 290°C (dec.) (ethanol-water); ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 13.80-13.50 (br s, 2H, both NH), 8.22 (s, 1H, C3-H), 8.00 (s, 1H, C8-H), 7.61 (d, J=8 Hz, 1H, C5-H), 7.29 (d, J=9 Hz, 1H, C4-H); hrms Calcd for $C_8H_6N_4$: 158.0592. Found: 158.0592.

2,6-Dihydro-2,3,6-trimethylbenzo[1,2-c:3,4-c']dipyrazole (8h). The residue obtained from treatment of 5.50 g (0.023 mol) of 7f with Pd/C for 18 h was flash chromatographed (7.5:92.5::2-propanol:methylene chloride) to give 2.20 g (48%) of 8h as a cream-colored crystalline solid, mp 128-134°C (toluene); ^1H nmr ($CDCl_3$) δ 8.28 (s, 1H, C8-H), 7.31 (d, J=8 Hz, 1H, C5-H), 6.95 (d, J=10 Hz, 1H, C4-H), 4.00 (s, 3H, NCH_3), 3.92 (s, 3H, NCH_3), 2.44 (s, 3H, CCH_3); ms (EI) m/z 200 (molecular ion); Anal. Calcd for $C_{11}H_{12}N_4 \cdot HCl$: C, 55.81; H, 5.53; N, 23.67. Found: C, 55.87; H, 5.64; N, 23.49.

1,6-Dihydro-3-methylbenzo[1,2-c:3,4-c']dipyrazole (8i). The residue obtained from treatment of 7q with Pd/C for 48 h was flash chromatographed (1:9::methanol:methylene chloride) to afford 2.30 g (31%) of 8i as a white solid, mp 277-280°C (toluene-ethyl acetate); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 12.50-12.00 (br s, 2H, both NH), 8.20 (s, 1H, C8-H), 7.50 (d, J=8 Hz, 1H, C5-H), 7.20 (d, J=8 Hz, 1H, C4-H), 2.55 (s, 3H, CH_3); hrms Calcd for $C_9H_8N_4$: 172.0749. Found: 172.0752.

2-[(2-(Phenylmethyl)hydrazino)methylene]-1,3-cyclopentanedione (15). A mixture of 1.30 g (6.66 mmol) of benzylhydrazine dihydrochloride, 2.80 ml (14.0 mmol) of 5 N sodium hydroxide solution and 10 ml of methanol was added to an ice cold solution of 1.00 g (6.53 mmol) of 14[10] in 20 ml of methanol. The mixture was heated at reflux for 2 h and concentrated, and the residue was partitioned between water and methylene chloride. The organic layer was dried ($MgSO_4$) and concentrated to provide 80.0 mg (53%) of 15 as a fluffy yellow solid, mp 164°C (dec.)(toluene-hexane); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.55 (d, J=1.5 Hz, 1H, vinyl), 7.30 (s, 5H, aromatic), 5.15 (br s, 2H, both NH), 4.05 (s, 2H, benzyl CH_2), 2.40-2.20 (m, 4H, CH_2CH_2); ms (EI) m/z 230 (molecular ion); Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.13; N, 12.09.

5,6-Dihydro-1-(phenylmethyl)-4(1H)-cyclopentapyrazolone (16). A solution of 1.00 g (4.34 mmol) of 15 and 50 mg of p-toluenesulfonic acid monohydrate in 200 ml of toluene was heated at reflux for 15 h. A Dean-Stark trap was used to collect water. Solvent was removed and the residue was flash chromatographed (1:9::methanol:methylene chloride) to give 0.41 g (44%) of 16. Another flash chromatography (1:19::methanol:methylene chloride) provided analytically pure 16, mp 92-93°C; ^{1}H nmr ($CDCl_3$) δ 7.55 (s, 1H, C3-H), 7.25 (s, 5H, phenyl), 5.20 (s, 2H, benzyl CH_2), 3.10-2.50 (m, 4H, CH_2CH_2); ms (CI) m/z 213 (M^++H), 241 (M^++29); 253 (M^++41); Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.59; H, 5.76; N, 13.24.

5,6-Dihydro-1-(phenylmethyl)-4(1H)-cyclopentapyrazolone-5-carboxaldehyde (17). A mixture of 1.46 ml (18.1 mmol) of ethyl formate, 1.44 g (36.0 mmol) of a 60% suspension of sodium hydride in mineral oil, ethanol (3 drops) and 150 ml of anhydrous tetrahydrofuran was stirred at 23°C for 30 min. A solution of 4.00 g (18.8 mmol) of 16 in 50 ml of anhydrous tetrahydrofuran was added dropwise and the reaction mixture was heated at reflux for 16 h. An additional 1.44 g (36.0 mmol) of a 60% suspension of sodium hydride in mineral oil was added and the reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled, diluted with water (150 ml) and washed with ether. The aqueous solution was acidified with dilute hydrochloric acid and the precipitate was collected to give 3.44 g (76%) of 17 as a tan oil which crystallized on standing, mp 171-172°C; ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.45 (s, 1H, C3-H), 7.35 (br s,

1H, C=CHOH), 7.20 (s, 5H phenyl), 5.25 (s, 2H, benzyl CH), 3.30-3.25 (m, 2H, C6-CH_2); ms (CI) m/z 241 (M^++1), 269 (M^++29), 281 (M^++41).

4,7-Dihydro-1-(phenylmethyl)-1H-cyclopenta[1,2-c:3,4-c']dipyrazole (18). To an ice cold solution of 0.500 g (2.08 mmol) of 17 in 25 ml of methanol was added 0.070 ml (2.21 mmol) of hydrazine, dropwise. The solution was heated at reflux for 2 h, cooled and stirred for 16 h. An additional 0.070 ml (2.21 mmol) of hydrazine was added and the solution was heated at reflux for 8 h. The solution was concentrated to leave 0.420 g (86%) of 18 as a red-orange solid, mp 61-72°C; ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.50 (s, 1H, pyrazole CH), 7.20 (s, 5H, phenyl), 7.10 (s, 1H, pyrazole CH), 5.30 (s, 2H, benzyl CH_2), 4.00 (br s, 1H, NH), 3.20 (s, 2H, C7-CH_2); hrms Calcd for $C_{14}H_{12}N_4$: 236.1062. Found: 236.1057.

4,7-Dihydro-1H-cyclopenta[1,2-c:3,4-c']dipyrazole (19). To a solution of 5.80 g (24.5 mmol) of 18 in 150 ml of tetrahydrofuran and 300 ml of liquid ammonia at -78°C was added 2.80 g (122 mmol) of sodium in small portions. The mixture was stirred at -32°C for 1.5 h and 10 g of ammonium chloride was added. The ammonia was allowed to evaporate, the mixture was filtered and the filter cake was washed with ethanol. The filtrate was concentrated and the residue was triturated with ethyl acetate to give 1.80 g (50%) of 19 as a tan oil which crystallized on standing, mp 180°C (dec.); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.45 (s, 1H, pyrazole CH), 7.30 (s, 1H, pyrazole CH), 4.20-3.70 (br s, 2H, both NH), 3.45 (s, 2H, CH_2); hrms Calcd for $C_7H_6N_4$: 146.0592. Found: 146.0603.

Treatment of 3c with Ethyl Diazoacetate. Preparation of 5,6,7,8-Tetrahydro-1-methyl-4(1H)-cycloheptapyrazolone (20). To a solution of 20.0 g (0.133 mol) of 3a and 28.4 ml (0.270 mol) of ethyl diazoacetate[13] in 400 ml of methylene chloride was added a solution of 33.2 ml (0.270 mol) of boron trifluoride ethereate in 50 ml of methylene chloride. The mixture was stirred at room temperature for 3 days and then cooled to 0°C and treated with excess saturated sodium bicarbonate solution. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and flash chromatographed (1:19::2-propanol:methylene chloride) to afford an amber oil. The oil was dissolved in a solution of 18.6 g of potassium hydroxide in 250 ml of water and heated at 100°C for 30 min. The solution was acidified with 5 N hydrochloric acid and heated briefly at 100°C. The solution was neutralized with sodium bicarbonate solution and extracted with methylene chloride. The extracts were concentrated to provide a mixture of 20, 21 and 22, which was diluted with 150 ml of dimethylformamide dimethyl acetal and heated at reflux for 1.5 h. Solvent was removed and the residue was flash chromatographed (1:9::acetone:methylene chloride followed by 1:9::methanol:methylene chloride) to provide[14] 1.00 g of 20 as a yellow, crystalline

solid, mp 93.5-94.5°C; ^{1}H nmr ($CDCl_3$) δ 7.85 (s, 1H, C3-H), 3.75 (s, 3H, CH_3), 3.05-2.55 (m, 4H, 2 C5-CH_2 and C8-CH_2), 2.33-1.70 (m, 4H, C6-CH_2 and C7-CH_2); ms (EI) m/z 164 (molecular ion).

5,6,7,8-Tetrahydro-5-acetyl-1-methyl-4(1H)-cycloheptapyrazolone (27). A 9.80-ml (0.070 mol) volume of diisopropylamine was slowly added to an ice cold solution of 27.0 ml (0.070 mol) of 2.6 M n-butyllithium (in hexane) in 200 ml of anhydrous tetrahydrofuran. The solution was cooled to -78°C and 5.50 g (0.034 mol) of 20 in 50 ml of tetrahydrofuran was added dropwise. The solution was stirred at -78°C for 20 min and 3.60 ml (0.050 mol) of acetyl chloride in 25 ml of anhydrous tetrahydrofuran was added dropwise. The mixture was warmed to -15°C and quenched by the slow addition of 600 ml of water. The layers were separated and the aqueous phase was washed with ether and acidified to pH 4 with 5 N hydrochloride acid. The slurry was extracted with methylene chloride and the organic extracts were dried ($MgSO_4$) and concentrated to give 4.10 g (58%) of 27 as a gummy yellow solid: ^{1}H nmr ($CDCl_3$) δ 7.90 (s, 1H, C3-H), 3.70 (s, 3H, NCH_3), 2.80 (t, J=6 Hz, 2H, CH_2), 2.60-2.30 (m, 2H, CH_2), 2.20 (s, 3H, CCH_3), 2.20-1.85 (m, 2H, C7-CH_2).

4,5,6,7-Tetrahydro-3,7-dimethyl-1H-cyclohepta[1,2-c:3,4-c']dipyrazole Hydrochloride (28). A solution of 4.00 g (19.4 mmol) of 27 and 0.7 ml (22 mmol) of hydrazine in 50 ml of methanol was heated at reflux for 30 min. The solution was concentrated and the residue was flash chromatographed (1:9::methanol:methylene chloride) to provide the cycloheptadipyrazole as a gummy yellow solid. This solid was dissolved in 2-propanol and treated with ethereal hydrochloric acid to give, after collection and drying, 2.90 g (61%) of 28 as a yellow solid, mp 277-280°C (dec.); ^{1}H nmr (D_2O) δ 7.60 (s, 1H, C9-H), 3.75 (s, 3H, NCH_3), 3.10-2.40 (m, 4H, C4-CH_2 and C6-CH_2), 2.30 (s, 3H, CCH_3), 2.10-1.60 (m, 2H, C5-CH_2); ms (EI) m/z 202 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_4 \cdot HCl$: C, 55.34; H, 6.33; N, 23.47. Found: C, 55.26; H, 6.26; N, 23.12.

5,6,7,8-Tetrahydro-5-(hydroxymethylene)-1-methyl-4(1H)-cycloheptapyrazolone (29). A 7.00 g (0.043 mol) quantity of 20 was combined with 2.30 g (0.095 mol) of dry sodium hydride, 12 ml of ethyl formate, 2 drops of ethanol and 180 ml of tetrahydrofuran. The mixture was heated at reflux, cooled and partitioned between water and ether. The aqueous layer was washed with ether and acidified to pH 5 with 1 N hydrochloric acid. The white precipitate which formed was collected and dried to give 7.30 g (88%) of 29, mp 133-135°C; ^{1}H nmr ($CDCl_3$) δ 16.50-16.20 (br d, 1H, OH), 8.10 (d, J=6 Hz, 1H, CHOH), 7.95 (s, 1H, C3-H), 3.80 (s, 3H, CH_3), 2.90 (t, J=6 Hz, 2H, CH_2), 2.60-2.30 (m, 2H, CH_2), 2.20-1.80 (m, 2H, C7-CH_2); ms (CI) m/z 193 (M^++1), 221 (M^++29), 233 (M^++41); Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.39; H, 6.24; N, 14.66.

4,5,6,7-Tetrahydro-7-methyl-1H-cyclohepta[1,2-c:3,4-c']dipyrazole (30). To a warm solution of 3.00 g (16.0 mmol) of 29 in 90 ml of methanol was slowly added 0.50 ml (16 mmol) of hydrazine. The solution was heated at reflux for 30 min, cooled and concentrated. The residue was triturated with warm ether to give 2.90 g (96%) of 30 as a tan solid, mp 153-155°C; ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.80 (s, 1H, C9-H), 7.20 (s, 1H, C3-H), 3.75 (s, 3H, CH_3), 3.10-2.65 (m, 4H, C4-CH_2 and C6-CH_2), 2.20-1.75 (m, 2H, C5-CH_2); ms (CI) m/z 189 (M^++1), 217 (M^++29), 229 (M^++41); Anal. Calcd for $C_{10}H_{12}N_4$·1.75 HCl: C, 47.65; H, 5.49; N, 22.23. Found: C, 47.90; H, 5.52; N, 22.39.

4,5,6,7-Tetrahydro-1,7-dimethyl-1H-cyclohepta[1,2-c:3,4-c']dipyrazole (31) and 4,5,6,7 Tetrahydro-2,7-dimethyl-2H-cyclohepta[1,2-c:3,4-c']dipyrazole (32). A solution of 1.1 ml (21 mmol) of methylhydrazine in 20 ml of methanol was added dropwise to an ice cold solution of 4.00 g (21.0 mmol) of 29 in 130 ml of methanol. The solution was heated at reflux for 2.5 h and concentrated to a dark oil. Flash chromatography (7.5:92.5::2-propanol:methylene chloride) gave 1.2 g (28%) of 31 as a yellow oil which crystallized on standing, mp 94-96°C; ^{1}H nmr ($CDCl_3$) δ 7.65 (s, 1H, C9-H), 7.15 (s, 1H, C3-H), 4.00 (s, 3H, N1-CH_3), 3.80 (s, 3H, N7-CH_3), 3.05-2.60 (m, 4H, C4-CH_2 and C6-CH_2), 2.20-1.75 (m, 2H, C5-CH_2); ms (CI) m/z 203 (M^++1), 231 (M^++29), 243 (M^++41); Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.24; H, 6.91; N, 27.69.

Also obtained from the chromatography was 2.3 g (54%) of 32, mp 119-121°C; ^{1}H nmr ($CDCl_3$) δ 7.80 (s, 1H, C9-H), 6.95 (s, 1H, C3-H), 3.75 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.05-2.60 (m, 4H, C4-CH_2 and C6-CH_2), 2.20-1.75 (m, 2H, C5-CH_2); ms (CI) m/z 203 (M^++1), 231 (M^++29), 243 (M^+41); Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 64.97; H, 6.96; N, 27.63.

4,5,6,7-Tetrahydro-1,6,6-trimethyl-4-oxo-1H-indazole-5-carboxaldehyde (34). A 23.8 ml (62.0 mmol) volume of 1.60 M n-butyllithium (in hexane) was slowly added to an ice cold solution of 8.70 ml (62.0 mmol) of N,N-diisopropylamine in 30 ml of anhydrous tetrahydrofuran. The solution was stirred at 0°C for 15 min and 10.8 ml (62.0 mmol) of hexamethylphosphoramide was added. The solution was stirred at 0°C for 15 min, cooled to -78°C and 5.00 g (28.1 mmol) of 33[2] in 150 ml of anhydrous tetrahydrofuran was added dropwise, followed by 8.90 ml (0.101 mol) of ethyl formate. The solution was allowed to warm to room temperature, and after stirring for 20 h was partitioned between water and methylene chloride. The aqueous layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The extracts were dried ($MgSO_4$) and concentrated. The resulting dark oil which crystallized on standing was flash chromatographed (1:9::acetone:methylene chloride) to give 3.04 g (52%) of 34 as light yellow crystals, mp 131-132°C (toluene-hexane); ^{1}H nmr ($CDCl_3$) δ 14.50 (d, J=10 Hz, 1H, C=CHOH), 7.80

(s, 1H, C3-H), 7.35 (d, J=10 Hz, 1H, C=CHOH), 3.75 (s, 3H, NCH_3), 2.70 (s, 2H, CH_2), 1.25 [s, 6H, $C(CH_3)_2$]; ms (EI) m/z 206 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.11; H, 6.85; N, 13.50.

1,4,5,6-Tetrahydro-4,4,6-trimethylbenzo[1,2-c:3,4-c']dipyrazole (35). A solution of 3.09 g (15.0 mmol) of 34 in 100 ml of methanol was treated with 0.60 ml (19 mmol) of hydrazine, and the solution was heated at reflux for 45 min, stirred at room temperature for 15 h and concentrated. The residue was triturated with ether to give 2.30 g (75%) of 35 as tan crystals, mp 232-234°C (ethyl acetate); ^{1}H nmr (DMSO-d_6) δ 7.52 (s, 1H, aromatic), 7.47 (s, 1H, aromatic), 3.77 (s, 3H, NCH_3), 2.69 (s, 2H, CH_2), 1.21 [s, 6H, $C(CH_3)_2$]; ms (EI) m/z 202 (molecular ion); Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.54; H, 7.05; N, 27.61.

1,4,5,6-Tetrahydro-1,4,4,6-tetramethylbenzo[1,2-c:3,4-c']dipyrazole (36) and 2,4,5,6-Tetrahydro-2,4,4,6-tetramethylbenzo[1,2-c:3,4-c']dipyrazole (37). A solution of 0.59 ml (11.1 mmol) of methylhydrazine in 20 ml of methanol was added dropwise to an ice cold solution of 2.22 g (10.8 mmol) of 34 in 80 ml of methanol. The solution was heated at reflux for 45 min and concentrated, and the residue was recrystallized from toluene to give 0.99 g (43%) of 37 as off-white crystals, mp 172-173°C; ^{1}H nmr ($CDCl_3$) δ 7.74 (s, 1H, C8-H), 7.11 (s, 1H, C3-H), 3.83 (s, 3H, NCH_3), 3.82 (s, 3H, NCH_3), 2.65 (s, 2H, CH_2), 1.27 [s, 6H, $C(CH_3)_2$]; ms (EI) m/z 216 (molecular ion); Anal. Calcd for $C_{12}H_{16}N_4 \cdot 0.5H_2O$: C, 63.97; H, 7.61; N, 24.87. Found: C, 64.25; H, 7.43; N, 25.11.

The mother liquor from the recrystallization was concentrated to provide 1.26 g (54%) of 36, mp 105-108°C (toluene); ^{1}H nmr ($CDCl_3$) δ 7.60 (s, 1H, C8-H), 7.28 (s, 1H, C3-H), 3.97 (s, 3H, N1-CH_3), 3.84 (s, 3H, N6-CH_3), 2.65 (s, 2H, CH_2), 1.27 [s, 6H, $C(CH_3)_2$]; hrms Calcd for $C_{12}H_{16}N_4$: 216.1375. Found: 216.1372; Anal. Calcd for $C_{12}H_{16}N_4$: C, 66.64; H, 7.46; N, 25.91. Found: C, 66.49; H, 7.42; N, 25.91.

1,4,5,7-Tetrahydro-1-methyl-4-oxothiopyrano[3,4-c']pyrazole-5-carboxaldehyde (39). A mixture of 8.80 g (0.220 mol) of sodium hydride (60% suspension in mineral oil), 8.90 ml (0.110 mol) of ethyl formate, 3 drops of ethanol and 400 ml of tetrahydrofuran was combined and stirred mechanically. A solution of 18.5 g (0.110 mol) of 38[15] in 100 ml of tetrahydrofuran was added dropwise and the mixture was heated at reflux for 4 h. The mixture was cooled, partitioned between ether and water and the aqueous phase was washed with methylene chloride and acidified with dilute hydrochloric acid. The resulting white solid was collected to give 16.2 g (75%) of 39, mp 158-159°C (ether-methylene chloride); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.90 (s, 1H, C3-H),

7.65 (br s, 1H, C=CHOH), 3.80 (s, 5H, CH_3 and CH_2); ms (EI) m/z 196 (molecular ion); Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.96; H, 4.11; N, 14.28. Found: C, 48.87; H, 4.21; H, 14.08.

5,6-Dihydro-6-methyl-1H-thiopyrano[3,2-c:5,4-c']dipyrazole (40). To a solution of 16.0 g (0.0815 mol) of 39 in 250 ml of methanol was added, dropwise, 3.50 ml (0.110 mol) of hydrazine. The solution was heated at reflux for 45 min, stirred at room temperature for 15 h and concentrated. The residue was triturated with ether to give 14.6 g (93%) of 40, mp 224-226°C (ethanol-water); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.70 (s, 1H, C8-H), 7.35 (s, 1H, C3-H), 4.00 (s, 2H, CH_2), 3.85 (s, 3H, CH_3); ms (CI) m/z 193 (M^++1), 221 (M^++29), 233 (M^++41); Anal. Calcd for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.15. Found: C, 49.95; H, 4.18; N, 29.28.

5,6-Dihydro-6-methyl-1H-thiopyrano[3,2-c:5,4-c']dipyrazole 4-oxide (41). A solution of 1.06 g (5.22 mmol) of 85% m-chloroperoxybenzoic acid in 30 ml of tetrahydrofuran was added dropwise to 1.00 g (5.20 mmol) of 40 in 20 ml of tetrahydrofuran at -15°C. The mixture was stirred at -15°C for 3 h and the precipitate was collected to give 1.01 g (93%) of 41 as a yellow solid, mp > 270°C (ethanol); ^{1}H nmr (DMSO-d_6) δ 8.40 (br s, 1H, C3-H), 7.85 (s, 1H, C8-H), 4.75 (d, J=16 Hz, 1H, C5-H), 4.00 (d, J=16 Hz, 1H, C5-H), 3.90 (s, 3H, CH_3); hrms Calcd for $C_8H_8N_4OS$: 208.0419. Found: 208.0413.

5,6-Dihydro-6-methyl-1H-thiopyrano[3,2-c:5,4-c']dipyrazole 4,4-dioxide (42). A solution of 7.92 g (39.0 mmol) of 85% m-chloroperoxybenzoic acid in 50 ml of methylene chloride was added dropwise to an ice cold solution of 4.00 g (20.8 mmol) of 40 in 100 ml of methylene chloride. The mixture was stirred at room temperature for 24 h and concentrated, and the residue was triturated with tetrahydrofuran to give 3.13 g (67%) of 42 as a yellow-orange solid, mp > 270°C (methanol); ^{1}H nmr (DMSO-d_6) δ 8.40 (s, 1H, C3-H), 7.80 (s, 1H, C8-H), 4.95 (s, 2H, CH_2), 3.85 (s, 3H, CH_3); ms (EI) m/z 224 (molecular ion); Anal. Calcd for $C_8H_8N_4O_2S$: C, 42.85; H, 3.59; N, 24.99. Found: C, 42.74; H, 3.74, N, 25.09.

5,6-Dihydro-6-methyl-1-(phenylmethyl)-2H-thiopyrano[3,2-c:5,4-c']dipyrazole (43). A solution of 2.95 g (15.1 mmol) of benzylhydrazine dihydrochloride and 6.00 ml (30.0 mmol) of 5 N sodium hydroxide solution in 50 ml of methanol was added, dropwise, to 2.70 g (13.8 mmol) of 39 in 50 ml of methanol. The mixture was heated to reflux for 5 h and concentrated, and the residue was flash chromatographed (1:19::methanol:methylene chloride) to give 2.69 g (69%) of 43, mp 204-206°C (ethanol-water); ^{1}H nmr ($CDCl_3$) δ 7.50-7.00 (m, 7H, aromatic), 5.45 (s, 2H, benzyl CH_2), 3.85 (s, 2H, SCH_2), 3.80 (s, 3H, CH_3); hrms Calcd for $C_{15}H_{14}N_4S$: 282.0939. Found: 282.0917.

5,6-Dihydro-1-methyl-2-(phenylmethyl)-2H-thiopyrano[3,2-c:5,4-c']dipyrazole 4-oxide (44). A solution of 1.29 g (6.35 mmol) of 85% m-chloroperoxybenzoic acid in 50 ml of tetrahydrofuran was added, dropwise, to 1.80 g (6.37 mmol) of 43 in 50 ml of tetrahydrofuran at -15°C. The mixture was maintained at -15°C for 3 h and the precipitate was collected to give 0.91 g (51%) of 44 as a white solid, mp 185-187°C (ethanol); ^{1}H nmr ($CDCl_3$) δ 8.00 (s, 1H, C3-H), 7.65 (s, 1H, C8-H), 7.35-7.05 (m, 5H, phenyl), 5.60-5.45 (m, 2H, benzyl CH_2), 4.40 (d, J=16 Hz, 1H, C5-H), 3.90 (s, 3H, CH_3), 3.70 (d, J=16 Hz, 1H, C5-H); ms (CI) m/z 299 (M^++1), 327 (M^++29), 339 (M^++41); Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78. Found: C, 60.41; H, 4.80; N, 18.68.

7-(Hydroxymethylene)-1,4-dioxaspiro[4.5]decan-8-one (46). To a mixture of 1.40 g (35.0 mmol) of 60% sodium hydride in mineral oil, 10 ml of ethyl formate, 1 drop of ethanol and 200 ml of tetrahydrofuran was added 5.00 g (32.0 mmol) of 1,4-cyclohexanedione (45). The mixture was heated at reflux for 2.5 h, cooled and partitioned between water and ether. The organic layer was extracted several times with 0.5 N sodium hydroxide and the combined aqueous phases were washed with ether and acidified to pH 4 with 5 N hydrochloric acid. This mixture was extracted with methylene chloride and the organic extracts were dried (magnesium sulfate) and concentrated. The resulting oil was bulb-to-bulb distilled (120°C/1 mm Hg) to give 4.00 g (68%) of 46 as a colorless oil; ^{1}H nmr ($CDCl_3$) δ 14.70 (br s, 1H, OH), 8.50 (s, 1H, C=CH-OH), 4.00 (s, 4H, OCH_2CH_2O), 2.70-2.40 (m, 4H, CH_2CH_2C=O), 2.00-1.70 (m, 2H, C6-CH_2); ms (CI) m/z 185 (M^++1), 213 (M^++29), 225 (M^++41); Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.43; H, 6.57.

1',4',6',7'-Tetrahydro-1'-methylspiro[1,3-dioxolane-2,5'-[5H]indazole] (47). To an ice cold solution of 2.00 g (10.9 mmol) of 46 in 40 ml of methanol was added 0.600 ml (11.3 mmol) of methylhydrazine. The solution was heated at reflux for 30 min and concentrated to afford an amber oil, which was flash chromatographed (ethyl acetate) to provide 1.60 g (76%) of 47 as a yellow oil; ^{1}H nmr ($CDCl_3$) δ 7.00 (s, 1H, C3'-H), 4.00 (s, 4H, OCH_2CH_2O), 3.80 (s, 3H, CH_3), 2.85 (t, J=6 Hz, 2H, C7'-CH_2), 2.70 (s, 2H, C4'-CH_2), 1.95 (t, J=6 Hz, 2H, C6'-CH_2); ms (CI) m/z 195 (M^++1), 223 (M^++29), 235 (M^++41); Anal. Calcd for $C_{10}H_{14}N_2O$: C, 61.83; H, 7.26; N, 14.43. Found: C, 61.61; H, 7.00; N, 14.29.

1,4,6,7-Tetrahydro-1-methyl-5H-indazol-5-one (48). A solution of 3.70 g (19.0 mmol) of ketal (47) in 100 ml of 10% aqueous acetic acid was heated at reflux for 3 h. Concentration left a dark oil which was flash chromatographed (ethyl acetate) to give a mixture of 48 and ethylene glycol, which was removed by distillation (1 mm Hg) to give 1.60 g (56%) of 48 as an orange

gum; ^{1}H nmr ($CDCl_3$) δ 7.10 (s, 1H, C3-H), 3.80 (s, 3H, CH_3), 3.30 (s, 2H, C4-CH_2), 3.15-2.80 (m, 2H, C7-CH_2), 2.75-2.40 (m, 2H, C6-CH_2); hrms Calcd for $C_8H_{10}N_2O$: 150.0793. Found: 150.0798.

4-[(Dimethylamino)methylene]-1,4,6,7-tetrahydro-1-methyl-5H-indazol-5-one (49). A solution of 1.10 g (7.32 mmol) of indazolone (48) in 25 ml of N,N-dimethylformamide dimethyl acetal was heated at reflux for 1.5 h. Excess reagent was removed by distillation and the residue was flash chromatographed (1:19::methanol:methylene chloride) to give 1.40 g (93%) of 49, which solidified on trituration with ether-hexane to a tan powder, mp 94-100°C; ^{1}H nmr ($CDCl_3$) δ 7.55 [s, 1H, CH=N(CH_3)$_2$], 7.00 (s, 1H, C3-H), 3.80 (s, 3H, N1-CH_3), 3.00 [s, 6H, N(CH_3)$_2$], 3.00-2.70 (m, 2H, C7-CH_2), 2.70-2.40 (m, 2H, C8-CH_2); hrms Calcd for $C_{11}H_{15}N_3O$: 206.1293 (M^++1). Found: 206.1304.

3,4,5,6-Tetrahydro-3-methylbenzo[1,2-c:4,3-c']dipyrazole (50). To a solution of 4.10 g (20.0 mmol) of 49 in 100 ml of methanol was added, dropwise, 1.00 ml (31.5 mmol) of hydrazine. The solution was heated at reflux for 30 min, treated with charcoal and filtered. The filtrate was concentrated and the residue was flash chromatographed (1:9::methanol:methylene chloride) to provide an amber oil, which was triturated with ether to give 2.60 g (74%) of 50 as a tan, crystalline solid, mp 150-156°C (toluene); ^{1}H nmr ($CDCl_3$) δ 7.45 (s, 1H, pyrazole CH), 7.20 (s, 1H, pyrazole CH), 3.80 (s, 3H, CH_3), 2.95 (s, 4H, CH_2CH_2); ms (EI) m/z 174 (molecular ion); Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 62.30; H, 5.77; N, 31.89.

3,6-Dihydro-3-methylbenzo[1,2-c:4,3-c']dipyrazole (51). A mixture of 3.80 g (21.8 mmol) of 50, 2.50 g of 5% Pd/C and 100 ml of decalin was heated at 195°C for 25 h. The mixture was cooled, diluted with hexane and filtered. The filter cake was stirred with 250 ml of methanol for 15 min and the mixture was filtered through celite. The filtrate was concentrated to give 2.60 g (69%) of 51 as a white solid, mp 220-227°C (dec.) (toluene); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 8.00 (s, 2H, aromatic), 7.35 (s, 2H, aromatic), 4.10 (s, 3H, CH_3); hrms Calcd for $C_9H_8N_4$: 172.0749. Found: 172.0743.

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12. A mixture of keto and enol forms was observed by ^{1}H nmr.
13. The hazardous properties of ethyl diazoacetate should be reviewed before using.
14. Also obtained from this chromatography was 4.60 g of a mixture of 21 and 22 as a viscous amber oil. This amber oil was dissolved in 150 ml of methanol and treated dropwise with 0.95 ml (0.030 mol) of hydrazine. The solution was heated at reflux for 6 h, concentrated, and the residue was triturated with ethanol-ether to provide 1.10 g of 4,5,6,7-tetrahydro-3-methyl-3H-cyclohepta[1,2-c:4,3-c']dipyrazole as a white solid, mp 201-204°C (toluene); ^{1}H nmr ($CDCl_3$ and DMSO-d_6) δ 7.60 (s, 1H, pyrazole CH), 7.50 (s, 1H, pyrazole CH), 3.70 (s, 3H, CH_3), 3.10-2.70 (m, 4H, 2 CH_2), 2.30-1.80 (m, 2H, CH_2; ms (EI) m/z 188 (molecular ion); Anal. Calcd for $C_{10}H_{14}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.76; H, 6.53; N, 29.40. The filtrate from the trituration was concentrated and triturated with toluene to provide 0.80 g of additional cycloheptadipyrazole. The filtrate was flash-chromatographed (1:9::methanol:methylene chloride) to provide 0.40 g of additional cycloheptadipyrazole plus 1.00 g of 3,4,5,6,7,8-hexahydro-3-methylcycloocta[1,2-c:4,3-c']dipyrazole as an orange solid, mp 146-152°C; ^{1}H nmr ($CDCl_3$) δ 7.60 (s, 1H, pyrazole CH), 7.45 (s, 1H, pyrazole CH), 3.80 (s, 3H, CH_3), 3.10-2.65 (m, 4H, C4-CH_2 and C7-CH_2), 2.05-1.65 (m, 4H, C5-CH_2 and C6-CH_2); hrms Calcd for $C_{11}H_{14}N_4$: 202.1218. Found: 202.1228.
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