Intramolecular Cycloaddition of 2-Allylphenylhydrazones[1)]

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Acid-catalyzed intramolecular cycloaddition of 2-allylphenylhydrazones is an effective method for the preparation of 2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole derivatives.

Keywords intramolecular; cationic; polar cycloaddition; 2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole; 2,3-dihydro-1*H*-pyrazolo[1,5-*a*]indole; 2-allylphenylhydrazone

In the course of studies on the amino-Claisen rearrangement,[2)] we required ethyl 7-allylindole-2-carboxylate **1**. For the synthesis of **1**, the hydrazone **2** was subjected to Fischer indolization[3)] with 10% sulfuric acid in ethanol, but no indole product was obtained. Detailed investigation of the reaction products revealed that cycloaddition had taken place between the olefinic bond and the hydrazone moiety, *i.e.* the 1*H*-pyrazolo[1,5-*a*]indole skeleton **3** had been formed.

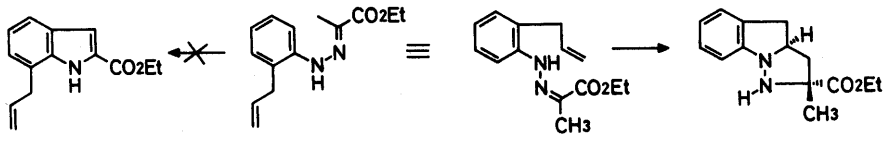
Although there are a few reports concerning the syntheses of this skeleton,[4)] the present method is especially valuable for the preparation of 2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole derivatives because of its simplicity and versatility. Also the framework of this compound can be regarded as a condensed indole derivative, so the generality of this intramolecular cycloaddition was further investigated. In this article we would like to report the details of our findings.

Preparation of 2-Allylphenylhydrazones We have prepared the hydrazones **6** and **7** according to the ordinary procedure, *i.e.* mixing of **4** and **5** in 60% acetic acid (Table I). The prepared hydrazones were labile to atmospheric oxygen[5)] and some were readily decomposed during storage[6)] and could not be purified by distillation without

TABLE I. Preparation of 2-Allylphenylhydrazones **6** and **7**

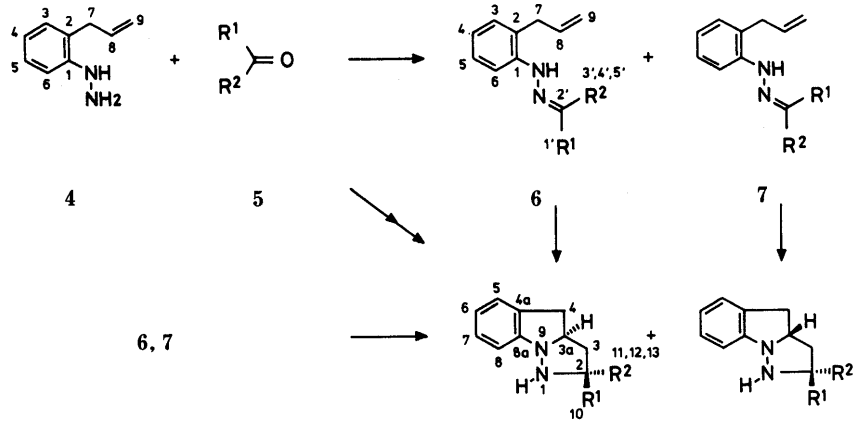
SM[a)]	Yield[b)]	**6** : **7**[d)]	SM[a)]	Yield[b)]	**6** : **7**[d)]
5a	0	—	**5f**	69	0 : 100
5b	c)		**5g**	90	19 : 81
5c	79	0 : 100	**5h**	74	**6h**=**7h**
5d	b)		**5i**	92	84 : 16
5e	48	**6e**=**7e**			

a) Starting material. *b*) The isolated yields (%). *c*) We were unable to isolate these hydrazones. *d*) Ratios of the isolated isomers.



1 2 3

Chart 1



4 5 6 7 8 9

	R^1	R^2		R^1	R^2		R^1	R^2
a	H	H	**d**	H	CO_2R	**g**	CH_3	CO_2Et
b	H	CH_3	**e**	CH_3	CH_3	**h**	Ph	Ph
c	H	Ph	**f**	CH_3	Ph	**i**	Ph	CO_2Me

R=H or CH_2CH_3

Chart 2

decomposition. We could not detect the formation of formaldehyde 2-allylhydrazone **6a**.[7] When a hydrazone was too labile to isolate, its formation and cycloaddition were carried out concomitantly by a one-pot procedure (*vide infra*). When geometrical isomers were possible, the preferred geometry was that rationalizable from steric considerations, although intramolecular hydrogen bonding could stabilize a *Z* isomer over an *E* isomer (*vide infra*). Geometrical assignments of **6g** and **7g** and **6i** and **7i** were carried out on the basis of their infrared (IR) and ultraviolet (UV) spectra. A *Z* isomer having intramolecular hydrogen bonding shows IR absorption of the carbonyl group at lower frequency and UV absorption at longer wavelength than those of the *E* isomer.[8] When there is a phenyl group in the hydrazone moiety, the hydrazone geometry is readily assigned from the nuclear magnetic resonance (NMR) spectra. The allylic methylene of **7i** (phenyl group is *cis* to the allyl group) is shielded and its signal appears at δ 3.0 ppm, but in **7c**, **7f** and **6i** (phenyl group is *trans* to the allyl group) it is deshielded to δ 3.4 ppm.

The isomerization between hydrazone stereoisomers,[8] **6g** and **7g**, and **6i** and **7i**, was investigated and the results are summarized in Table II. The *Z* and *E* isomers could interconvert readily under acidic and neutral conditions with heating. Under these conditions the *Z* isomer with intramolecular hydrogen bonding was preferred over the *E* isomer, as expected.[8]

Intramolecular Cycloaddition of 2-Allylphenylhydrazones The cycloaddition reaction was carried out with 10% sulfuric acid in ethanol at refluxing temperature (reaction condition A). Dimethoxyethane was used when the reaction was slow and ester exchange was possible in ethanol (reaction condition B). The results are summarized in Table III. The hydrazones which could not be isolated were formed and reacted in the same flask (one-pot procedure). For this one-pot procedure two reaction conditions, 60% acetic acid (reaction condition C) and 0.2→10% sulfuric acid in ethanol (reaction condition D) were used. This procedure was also applied to the other hydrazones and the results are included in Table IV. Among the two reaction conditions, the reaction condition which gave the better yield is listed.

In reaction condition D, **5b** yielded a small amount of **9b**, the isomer of **8b**. But in reaction condition C, it did not give **9b** but 2-methyl-3,3a-dihydro-4*H*-pyrazolo[1,5-*a*]indole, the oxidized product of **8b** and **9b**. The reaction of **5f** gave **8f** as the minor product in reaction condition C but no **8f** was obtained in reaction condition D. The formations of these minor products from **5b** and **5f** were dependent upon the reaction conditions. An attempt at the formation of the hydrazone **6a** (=**7a**) and the subsequent one-pot procedure gave only an intractable mixture.[9] The one-pot procedure was extremely useful for the cycloaddition of labile hydrazones from **5b** and **5d**. It also gave a better yield of the cycloadduct when used to prepare hydrazones from **5e** and **5f**.

Structural Elucidation of the Cycloaddition Products The structures of the cycloaddition products were deduced from their spectral behaviors. The principal framework was proved by chemical transformation into the known compound.

In the mass spectrum (MS), the cycloaddition products had the same molecular ion peak (M^+) as their starting hydrazones. The carbon framework carrying protons was deduced from irradiation experiments in the ^{1}H-NMR spectra. For instance, irradiation at δ 3.98 ppm (3a-H of **8g**) revealed two distinct AB type signals at δ 2.09 (J=12.9 Hz) and 3.20 (J=15.6 Hz) ppm due to C-4 methylene protons. Similar results were obtained for the cycloadducts derived from ketone hydrazones, regardless of the configurational differences. In the cycloadducts from aldehyde hydrazones, the C-2 proton appeared at lower magnetic field than 3a-H as a multiplet owing to coupling with the C-3 methylene

Table II. Isomerization of 2-Allylphenylhydrazones **6** and **7**

SM[a]	R.C.[b]	6[c]	7[c]	Cycloadduct[c]	6 : 7[d]
6g	A/19 h	33.2	38.0	21.4	47 : 53
6g	B/6.5 h	82.6	10.2	—	81 : 11
7g	A/14 h	44.3	44.0	9.0	50 : 50
7g	B/10.5 h	45.3	33.8	15.9	57 : 43
6i	A/18 h	79.9	19.7	—	80 : 20
6i	B/6 h	69.8	15.1	—	82 : 18
7i	A/20 h	66.4	32.8	—	67 : 33
7i	B/6 h	80.6	19.2	—	81 : 19

a) Starting material. *b*) Reaction conditions A: A solution of hydrazone in dichloromethane (*ca.* 0.1 M) containing concentrated HCl (1 drop/ml) was stirred at room temperature for the period indicated. B: A solution of hydrazone in xylene (*ca.* 0.4 M) was refluxed for the time indicated (bath temperature 160 °C). *c*) The isolated yields (%). *d*) The ratios of the isolated products.

Table III. Cycloaddition of 2-Allylphenylhydrazones **6** and **7**

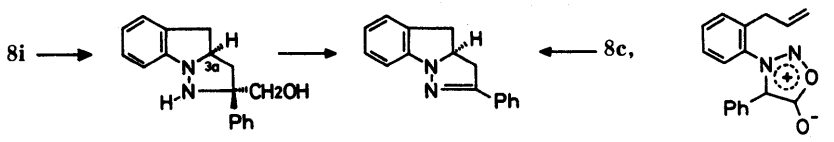
SM[a]	RC[b]	Yield[c]	8 : 9[d]
7c	A/3 h	86	100 : 0
6e=**7e**	A/1.5 h	54	**8e**=**9e**
7f	A/1.5 h	30	0 : 100
6g	A/2 h	86	81 : 19
7g	A/2 h	94	82 : 18
6h=**7h**	B/1.5 h	20	**8h**=**9h**
6i	B/1.5 h	85	80 : 20
7i	B/1.5 h	82	67 : 33

a) Starting material. *b*) Reaction conditions A: 10% sulfuric acid in ethanol. B: 10% sulfuric acid in dimethoxyethane. In both cases, the reaction mixture was refluxed for the time indicated under a nitrogen atmosphere. *c*) The isolated yields (%). *d*) The ratios obtained from the integration of ^{1}H-NMR spectra.

Table IV. One-Pot Procedure for the Cycloaddition

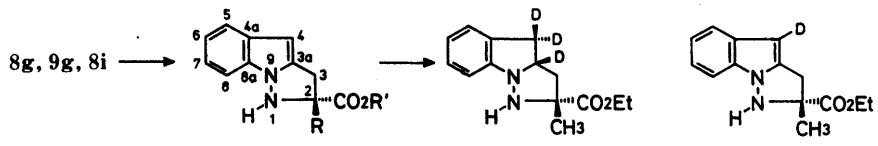
SM[a]	RC[b]	Yield[c]	8 : 9[d]
5a	C, D	0	—
5b	D/0.5 h	75	93 : 7
5c	D/1 h	86	100 : 0
5d	D/0.5 h	43[e]	100 : 0
5e	D/2 h	80	**8**=**9**
5f	C/2 h	60	5 : 95
5g	D/1.5 h	80	80 : 20
5h	D/1 h	0[f]	—
5i	D/1.5 h	8[g]	75 : 25

a) Starting material. *b*) Reaction conditions C: 60% acetic acid. D: 0.2→10% sulfuric acid in ethanol. Under both conditions the reaction mixture was heated to 110 °C (bath temperature) for the time indicated. *c*) The isolated yields (%). *d*) The ratios were obtained from the integration of ^{1}H-NMR spectra of the crude products. The ratios of the products derived from **5g** and **5i** were calculated from the isolated yields. *e*) The product was the ethyl ester. *f*) No cycloaddition product was obtained. The product was the hydrazone (50% yield). *g*) Reaction was incomplete. Major products were the hydrazones **6i** (58%) and **7i** (19%).



12 10 11

Chart 3



13 14 15

13a : R = Me, R' = Et

13b : R = Ph, R' = Me

Chart 4

group. Despite this complication, the carbon framework of the cycloadducts **8c** and **8i** was similarly deduced from the ^{1}H-NMR spectra and was proved by chemical conversion into **10** as shown in Chart 3.

When **8c** was subjected to Swern oxidation,[10] it was dehydrogenated to **10** which was identical with the product obtained by the photolysis of sydnone **11**.[4b] The reduction of **8i** with lithium aluminum hydride and the periodic cleavage of the resulting alcohol **12** also yielded **10**. The product **10** was a by-product (2%) when the cycloaddition of **7c** was carried out without great care to protect the reaction mixture from atmospheric oxygen.

The configuration of the cycloadducts was determined by detailed analyses of their NMR spectra. Looking at the stereomodel, R^1 of **8** and R^2 of **9** are shielded by the benzene ring and R^2 of **8** and R^1 of **9** are in the deshielded area. These distinct differences are nicely reflected in the chemical shifts of the R^1 and R^2 groups. Thus the signals of the methyl group of **8g** (R^1 = Me, δ 1.26 ppm) appears at 0.2 ppm higher field than that of **9g** (R^1 = Me, δ 1.48 ppm) and the ethyl signals of ester **8g** ($R^2 = COOCH_2CH_3$, δ 4.21 and 1.29 ppm) are at 0.3—0.4 ppm lower field than those of **9g** ($R^2 = COOCH_2CH_3$, δ 3.82 and 0.99 ppm). When a set of stereoisomers was in hand, their configurational assignments were straightforward. The configuration of **8d** was determined by the observation that the ethyl group of **8d** resonated at δ 4.21 (q) and 1.27 (t) ppm. Among the cycloaddition products the configuration of the cycloadduct **8c** derived from benzaldehyde **5c** was not assigned by analysis of the ^{1}H-NMR spectrum. The coupling constant (J = 8.1 Hz) of 2-H (δ 4.05 ppm as a doublet) did not allow us to determine the C-2 configuration. Thus, the structure of **8c** was established by X-ray crystallographic determination.[11]

In order to introduce the double bond, a mixture of **8g** and **9g** was treated with palladium chloride in the presence of triethylamine[12] and **13a** was obtained in 50% yield. Also **8i** was dehydrogenated with palladium on charcoal in xylene at refluxing temperature to give **13b** in 90% yield (Chart 4). These products had almost the same UV absorption patterns as 2-methylindole. The product **13a** was also obtained as a by-product when Fischer indolization of the hydrazone mixture **6g** and **7g** was carried out by using dry hydrogen chloride in ethanol. The reduction of **13a** and **13b** with sodium cyanoborohydride in methanolic hydrogen chloride[13] gave products **8g** and **8i**, respectively, which were slightly contaminated with their stereoisomers according to NMR analyses. When **13a** was reduced with sodium cyanoborodeuteride in AcOD–deuterium oxide, the major product was not isolated in pure form but the isolated minor product **14** contained three deuteriums (Chart 4). The presence of three deuteriums in the product proves that no double bond isomerization took place during the reduction. The incorporation of three deuteriums into **14** can be rationalized by the initial exchange of 4-H with deuterium to give **15** and the subsequent reduction of **15** with sodium cyanoborodeuteride. The formation of **15** was confirmed in a separate experiment. When **13a** was dissolved in AcOD, 4-H of **13a** was exchanged with deuterium in a few minutes. The incorporated deuterium was readily replaced with a proton during column chromatography. These features of 4-H on **13a** are similar to those of 3-H on indoles, which can be readily exchanged with deuterium by general acid catalysis.[14]

Reaction Mechanism During the investigation of the hydrazone isomerization, thermal cycloaddition of **7g** was observed (Table II). The thermal cycloaddition of hydrazone is proposed to take place *via* the azomethine-imine dipole which is derived by 1,2-proton shift of hydrazone.[15] As we have observed, thermal cycloaddition is slow under neutral conditions, but is accelerated by acid catalysis.[16] Our acid-catalyzed cycloadditions proceed *via* the protonated azomethine-imine species and can be categorized as ($3^+ + 2$) type polar cycloaddition.[17] They can be deduced to be concerted reactions by following the same series of reactions.[18] Providing that the above cycloaddition of hydrazone has similar stereochemical requirements to the ordinary 1,3-dipolar cycloaddition,[19] *i.e.* parallel-plane approach, the hydrazone **6** should produce the cycloadduct **8**, and **7** should afford **9** unequivocally. From the steric requirement for cycloaddition, no crossover is possible in these cycloadditions. However, the hydrazones isomerize more readily than they undergo cycloaddition (Table II), so even a stereochemically pure hydrazone did not give a sole

product but a mixture of isomeric cycloadducts (Tables III and IV). Except for **8b** and **8c** the kinetic products are preferentially formed and they are derived from the thermodynamically more stable hydrazones. The cycloadducts **8b** and **8c** are thermodynamic products and are derived solely from the thermodynamically less stable hydrazones. There are reports which deal with the equilibrium between cycloaddition and retrocycloaddition reactions.[20] The exposure of the cycloadducts **8i** and **9i** to acidic conditions did not lead to any contamination with other isomers and no change of ratio between **8b** and **9b** was observed under thermal or acidic reaction conditions. These negative observations tend to rule out the possibility that the formation of **8b** and **8c** is thermodynamically controlled by the presence of an equilibrium. The reaction mechanism leading to **8b** and **8c** remains open to discussion.

Conclusion

We have found a versatile method for the construction of 1*H*-pyrazolo[1,5-*a*]indole derivatives. Our method is especially valuable for the preparation of 2-disubstituted 2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole derivatives. The reaction used was the intramolecular cationic polar cycloaddition between a hydrazone and an olefinic double bond. This reaction constitutes the first reported example of the cycloaddition reaction between an aliphatic ketone phenylhydrazone and a non-activated double bond.[21] Cycloadditions involving ketone hydrazones are quite rare, even with an activated double bond.[20c]

Experimental

All melting points (mp) are uncorrected. Spectra were measured with the following spectrometers: ^{1}H- and ^{13}C-NMR spectra, JEOL JNM-FT 200 (measured in $CDCl_3$ containing tetramethylsilane as an internal standard); high-resolution MS, Hitachi RMU-7MG double focus[22]; UV, Shimadzu UV-200; IR, Hitachi 215 grating or Perkin-Elmer FT-IR 1720. Unless otherwise noted, each organic extract was dried over anhydrous sodium sulfate or magnesium sulfate and the crude product was purified by column chromatography on SiO_2.

2-Allylphenylhydrazine, 4 2-Allylaniline[23] (4.65 g, 35 mmol) was dissolved in a solution of 35% hydrochloric acid (16 ml) and water (27 ml) and treated with a solution of sodium nitrite (2.88 g) in water (5 ml) at below 5 °C. Excess reagent was decomposed by the addition of aminosulfonic acid. This solution was poured into a solution of stannous chloride dihydrate (17.4 g, 77.6 mmol) in 35% hydrochloric acid (17.4 g) which had been precooled to 0 °C. The reaction mixture was stirred at 0 °C for 1 h then suction-filtered. The collected white precipitate was treated with 20% sodium hydroxide and extracted with ether (30 ml × 3) to give the crude product as an oil (2.704 g, 52.2% yield). Purification was carried out as the hydrochloride. **4**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1635, 1600, 1498, 920. ^{1}H-NMR δ: 3.25 (2H, d, J=6.3 Hz, 7-H), 3.46 (2H, br, NH_2), 5.02, 5.08, 5.12 (2H, each m, 9-H), 5.91 (1H, tdd, J=60.3, 10.3, 16.6 Hz, 8-H), 6.78 (1H, t, J=7.3 Hz, 4-H), 6.99 (1H, d, J=8.3 Hz, 6-H), 7.03 (1H, d, J=7.0 Hz, 3-H), 7.22 (1H, t, J=7.7 Hz, 5-H). ^{13}C-NMR δ: 36.6 (C-7), 110.2 (C-6), 116.3 (C-9), 119.0 (C-4), 123.2 (C-2), 127.6 (C-5), 129.8 (C-3), 135.7 (C-8), 149.0 (C-1).

Hydrochloride: mp 127.5—130 °C (dec.) *Anal.* Calcd for $C_9H_{13}ClN_2$: C, 58.54; H, 7.09; N, 15.17. Found: C, 58.37; H, 7.07; N, 15.16.

Ethyl Pyruvate (*ZE*)-2-Allylphenylhydrazones, 6g and 7g: General Procedure A solution of ethyl pyruvate (2.74 g, 23.6 mmol) and 2-allylphenylhydrazine (1.75 g, 11.8 mmol) in 60% acetic acid (18 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water (45 ml) and extracted with ether three times. The extract was washed with water, 1 M sodium bicarbonate and saturated brine successively. The crude product (3.17 g) was separated to give the *Z*-isomer **6g** (0.48 g, 16.6% yield) and the *E*-isomer **7g** (2.05 g, 70.8%).

Z-Isomer **6g**: mp 26.0—26.5 °C. HRMS Calcd for $C_{14}H_{18}N_2O_2$: 246.1367. Found: 246.1372. MS *m/z*: 246 (M^+, 5), 173 (13), 132 (11), 131 (10), 130 (100), 117 (6). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3280, 1677, 1555, 1150. UV λ_{max}^{EtOH} nm (log ε): 204 (4.20), 239 (3.95), 298 (3.51), 350 (4.17). ^{1}H-NMR δ: 1.34 (3H, t, J=7.0 Hz, CH_2–C$\underline{H}_3$), 2.16 (3H, s, C$\underline{H}_3$), 3.36 (2H, d, J=6.1 Hz, 7-H), 4.27 (2H, q, J=7.0 Hz, O–CH_2–CH_3), 5.07, 5.13, 5.15 (2H, each m, 9-H), 5.98 (1H, tdd, J=6.1, 9.7, 17.3 Hz, 8-H), 6.90 (1H, dt, J=1.2, 7.3 Hz, 4-H), 7.10 (1H, dd, J=1.2, 7.4 Hz, 3-H), 7.21 (1H, dt, J=1.2, 7.5 Hz, 5-H), 7.61 (1H, d, J=8.0 Hz, 6-H). ^{13}C-NMR δ: 14.2 (5′-C), 19.4 (1′-C), 35.4 (C-7), 60.5 (4′-C), 113.4 (C-6), 116.5 (C-9), 121.4 (C-4), 123.9 (C-2), 126.1 (2′-C), 127.6 (C-5), 129.9 (C-3), 135.1 (C-8), 141.5 (C-1), 163.8 (3′-C).

E-Isomer **7g**: mp 58.5—59.5 °C (hexane). IR ν_{max}^{KBr} cm^{-1}: 3400, 1700, 1582, 1252, 1150, 758. UV λ_{max}^{EtOH} nm (log ε): 205 (4.45), 231 (4.13), 293 (4.08), 318 (4.25). ^{1}H-NMR δ: 1.37 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.02 (3H, s, CH_3), 3.42 (2H, d, J=6.1 Hz, 7-H), 4.30 (2H, q, J=7.0 Hz, O–C$\underline{H}_2$–CH_3), 5.14, 5.18, 5.22 (2H, each m, 9-H), 5.96 (1H, tdd, J=6.1, 10.7, 16.6 Hz, 8-H), 6.92 (1H, t, J=7.4 Hz, 4-H), 7.10 (1H, d, J=7.3 Hz, 3-H), 7.25 (1H, t, J=7.7 Hz, 5-H), 7.64 (1H, d, J=7.0 Hz, 6-H), 7.82 (1H, br, NH). ^{13}C-NMR δ: 10.6 (1′-C), 14.3 (5′-C), 37.0 (C-7), 61.1 (4′-C), 114.7 (C-6), 116.7 (C-9), 121.8 (C-4), 123.1 (C-2), 128.0 (C-5), 130.3 (C-3), 133.4 (2′-C), 136.0 (C-8), 141.7 (C-1), 165.2 (3′-C). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.04; H, 7.36; N, 11.35.

Benzaldehyde (*E*)-2-Allylphenylhydrazone, 7c Reddish brown oil, readily darkened on standing. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3341, 3065, 3011, 1605, 1587. ^{1}H-NMR δ: 3.38 (2H, d, J=6.1 Hz, 7-H), 5.17, 5.19 (2H, m, 9-H), 6.00 (1H, tdd, J=6.1, 10.5, 16.8 Hz, 8-H), 6.85 (1H, dt, J=1.2, 7.3 Hz, 4-H), 7.08 (1H, br d, J=7.1 Hz, 3-H), 7.21—7.70 (9H, m, Ar-H + NH). ^{13}C-NMR δ: 36.3 (C-7), 113.6 (C-6), 116.6 (C-9), 120.0 (C-4), 121.8 (C-2), 126.2 (d, 2 × C), 127.9 (C-5), 128.4 (d), 128.5 (d, 2 × C), 130.1 (C-3), 135.3 (s), 136.3 (C-8), 138.19 (s), 142.9 (C-1).

Acetone 2-Allylphenylhydrazone, 6e (=7e) Brown oil. IR ν_{max}^{film} cm^{-1}: 3365, 2979, 2910, 1633, 1589, 1509, 1467, 1245, 1135, 749. ^{1}H-NMR δ: 1.80 (3H, s, CH_3), 2.04 (3H, s, CH_3), 3.35 (2H, d, J=6.1 Hz, 7-H), 5.11, 5.18 (2H, m, 9-H), 5.93 (1H, tdd, J=6.1, 9.5, 15.6 Hz, 8-H), 6.78 (1H, dt, J=1.1, 7.3 Hz, 4-H), 6.96 (1H, br s, NH), 7.04 (1H, dd, J=1.1, 7.4 Hz, 3-H), 7.19 (1H, dt, J=1.1, 7.8 Hz, 5-H), 7.49 (1H, d, J=8.1 Hz, 6-H). ^{13}C-NMR δ: 15.8 (1′-C), 25.2 (3′-C), 37.1 (C-7), 113.1 (C-6), 116.2 (C-9), 119.2 (C-4), 121.8 (C-2), 127.8 (C-5), 130.0 (C-3), 136.3 (C-8), 144.1 (2′-C), 144.4 (s).

Acetophenone (*E*)-2-Allylphenylhydrazone, 7f Oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3365, 3064, 3010, 1683, 1634, 1587, 1494. ^{1}H-NMR δ: 2.17 (3H, s, CH_3), 3.43 (2H, d, J=6.1 Hz, 7-H), 5.18—5.28 (2H, m, 9-H), 5.98 (1H, tdd, J=6.1, 10.5, 16.8 Hz, 8-H), 6.84 (1H, dt, J=1.2, 7.3 Hz, 4-H), 7.09 (1H, dd, J=1.2, 7.3 Hz, 3-H), 7.16—7.97 (8H, m, Ar-H). ^{13}C-NMR δ: 12.3 (C-1′), 37.1 (C-7), 113.6 (C-6), 116.5 (C-9), 119.9 (C-4), 122.3 (C-2), 125.5 (d, 2 × C), 127.9 (C-5), 128.3 (d, 3 × C). 130.1 (C-3), 133.0 (s), 136.3 (C-8), 139.1 (s), 143.5 (C-1).

Benzophenone 2-Allylphenylhydrazone, 6h (=7h) mp 63.5—64.0 °C (methanol–ethanol). MS *m/z*: 312 (M^+, 9), 235 (6), 182 (19), 132 (27), 131 (13), 130 (100), 77 (23). IR ν_{max}^{KBr} cm^{-1}: 3341, 3055, 1602, 1587, 1508, 1256, 1132, 751, 701. ^{1}H-NMR δ: 3.01 (2H, d, J=6.4 Hz, 7-H), 4.36 (1H, dd, J=1.5, 17.1 Hz, 9-H), 4.66 (1H, dd, J=1.5, 10.3 Hz, 9-H), 5.54 (1H, tdd, J=6.4, 10.1, 16.1 Hz, 8-H), 6.79 (1H, t, J=7.3 Hz, 4-H), 6.98 (1H, d, J=6.1 Hz, 3-H), 7.17—7.63 (11H, m, Ar-H), 7.75 (1H, d, J=8.3 Hz, 6-H). ^{13}C-NMR δ: 36.6 (C-7), 113.1 (C-6), 116.0 (C-9), 119.7 (C-4), 122.2 (C-2), 126.3 (d, 2 × C), 127.8 (d), 127.9 (C-5), 128.1 (d, 2 × C), 129.0 (d, 2 × C), 129.0 (d), 129.6 (d, 2 × C), 130.0 (C-3), 133.4 (s), 135.2 (C-8), 138.3 (s), 142.9 (s), 145.0 (C-1). *Anal.* Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.75; H, 6.41; N, 8.91.

Methyl Benzoylformate 2-Allylphenylhydrazones *Z*-Isomer, 6i mp 91.5—93.0 °C. IR ν_{max}^{KBr} cm^{-1}: 3330, 1680, 1530, 1230, 1190, 1157, 762. ^{1}H-NMR δ: 3.44 (2H, d, J=5.8 Hz, 7-H), 3.85 (3H, s, OCH_3), 5.13 and 5.20 (2H, each m, 9-H), 6.03 (1H, tdd, J=5.8, 10.0, 17.8 Hz, 8-H), 6.96 (1H, t, J=7.5 Hz, 4-H), 7.14 (1H, d, J=7.0 Hz, 3-H), 7.243 (1H, t, J=7.0 Hz, 5-H), 7.30—7.41 (3H, m, Ar-H), 7.64 (2H, d, J=7.0 Hz, Ar-H), 7.70 (1H, d, J=8.0 Hz, 6-H). ^{13}C-NMR δ: 35.4 (C-7), 51.7 (C-4′), 114.1 (C-6), 116.7 (C-9), 122.4 (C-4), 124.6 (C-2), 127.5 (d), 127.7 (C-5), 127.8 (d, 2 × C), 128.3 (s), 128.6 (d, 2 × C), 130.0 (C-3), 134.8 (C-8), 136.5 (s), 141.0 (C-1), 164.0 (s). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.51. Found: C, 73.37; H, 6.15; N, 9.44.

E-Isomer **7i**: mp 104—105.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3320, 1718, 1557, 1237, 950, 750. ^{1}H-NMR δ: 3.06 (2H, d, J=6.1 Hz, 7-H), 3.85 (3H, s, OCH_3), 4.37 (1H, d, J=17.0 Hz, 9-H), 4.68 (1H, d, J=10.0 Hz, 9-H), 5.56 (1H, tdd, J=6.1, 10.0, 17.0 Hz, 8-H), 6.90 (1H, t, J=7.3 Hz, 4-H), 7.07 (1H, d, J=7.0 Hz, 3-H), 7.26 (1H, t, J=8.0 Hz, 5-H), 7.28—7.33 (2H, m, Ar-H), 7.45—7.53 (3H, m, Ar-H), 7.71 (1H, d, J=8.0 Hz, 6-H), 8.25 (1H, br, NH). ^{13}C-NMR δ: 36.4 (C-7), 52.2 (C-4′), 114.7 (C-6), 116.3 (C-9), 122.1

(C-4), 123.5 (C-2), 128.0 (C-5), 128.9 (d, 2 × C), 129.5 (d, 3 × C), 130.2 (C-3), 130.4 (s), 135.1 (C-8+s), 141.0 (C-1), 164.9 (s). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.51. Found: C, 73.49; H, 6.18; N, 9.52.

Isomerization of Hydrazone 7g: General Procedure a) Acid-catalyzed isomerization: The *E*-isomer **7g** (500 mg, 2.03 mmol) was dissolved in dichloromethane (20 ml) and treated with 35% hydrochloric acid (0.30 ml) for 14 h at room temperature. After addition of water and sodium hydrogen carbonate, the organic phase was collected. The crude product (500 mg) was separated to give the *Z*-isomer **6g** (221.7 mg, 44.3%), *E*-isomer **7g** (219.9 mg, 44.0%) and cycloadduct **8g** (44.9 mg, 9.0%). b) Thermal isomerization: A solution of the *E*-isomer **7g** (500 mg, 2.03 mmol) in xylene (10 ml) was heated at 160 °C (bath temperature) for 10.5 h. The solvent was evaporated off and the residue (493 mg) was chromatographed to separate the *Z*-isomer **6g** (226.4 mg, 45.3%), the *E*-isomer **7g** (165.1 mg, 33.0%) and the cycloadduct **8g** (15.9%).

Cycloaddition of the Hydrazone 7g: General Procedure a) With 10% sulfuric acid in ethanol: The *E*-isomer **7g** (1.95 g, 7.92 mmol) was dissolved in 10% (w/v) sulfuric acid in ethanol (45 ml) and the solution was refluxed (bath temperature 110 °C) for 2 h. After dilution with water the solution was basified with sodium carbonate then extracted with ether three times. Column chromatography of the crude product (1.84 g) was repeated to obtain **8g** (1.49 g, 76.3%) and **9g** (337 mg, 17.3%).

(2*RS*,3a*SR*)-2-Carboethoxy-2-methyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8g) Oil. HRMS Calcd for $C_{14}H_{18}N_2O_2$: 246.1367. Found: 246.1379. MS *m/z*: 246 (M^+, 45.3), 173 (51.8), 156 (5.8), 146 (8.1), 132 (100), 131 (49.3), 130 (24.7), 117 (16.3), 42 (25.8). UV λ_{max}^{EtOH} nm (log ε): 287 (3.31), 239 (3.86), 210 (4.10); UV $\lambda_{max}^{EtOH+HCl}$ nm (log ε): 280 (3.14), 232 (3.73), 209 (4.05). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3315, 2850, 1723, 1610, 1598, 1477, 1462, 1285, 1116, 1020, 885, 860. ^{1}H-NMR δ: 1.26 (3H, s, CH_3), 1.29 (3H, t, *J* = 7.0 Hz, CH_2–CH_3), 1.67 (1H, ABX type, J_{AB} = 12.9, J_{AX} = 10.0 Hz, 3-H), 2.50 (1H, ABX type, J_{BX} = 6.8 Hz, 3-H), 2.92 (1H, A′B′X′ type, $J_{A'B'}$ = 15.6, $J_{A'X'}$ = 0, 4-H), 3.11 (1H, A′B′X′ type, $J_{B'X'}$ = 7.8 Hz, 4-H), 3.91 (1H, m, 3a-H), 4.21 (2H, q, *J* = 7.0 Hz, O–CH_2–CH_3), 5.35 (1H, NH), 6.85 (1H, dt, *J* = 0.9, 7.3 Hz, 6-H), 7.00 (1H, d, *J* = 7.5 Hz, 8-H), 7.08 (1H, d, *J* = 7.0 Hz, 5-H), 7.14 (1H, t, *J* = 7.5 Hz, 7-H). ^{13}C-NMR δ: 14.1 (C-13), 27.0 (C-10), 32.7 (C-4), 45.0 (C-3), 61.6 (C-12), 65.9 (C-3a), 67.9 (C-2), 114.3 (C-8), 121.4 (C-6), 125.1 (C-5), 126.7 (C-4a), 127.6 (C-7), 154.2 (C-8a), 176.0 (C-11).

(2*SR*,3a*SR*)-2-Carboethoxy-2-methyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (9g) Oil. HRMS Calcd for $C_{14}H_{18}N_2O_2$: 246.1366. Found: 246.1353. MS *m/z*: 246 (M^+, 41.9), 173 (55.5), 156 (10.0), 146 (10.9), 132 (100), 131 (49.7), 130 (31.9), 117 (18.6), 77 (12.5). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 2855, 1727, 1610, 1598, 1477, 1462, 1350, 1125, 1021, 890, 860. ^{1}H-NMR δ: 0.99 (3H, t, *J* = 7.0 Hz, CH_2–CH_3), 1.48 (3H, s, CH_3), 2.02 (1H, dd, *J* = 8.0, 12.9 Hz, 3-H), 2.51 (1H, dd, *J* = 7.5, 12.9 Hz, 3-H), 3.01 (1H, dd, *J* = 1.9, 15.6 Hz, 4-H), 3.17 (1H, dd, *J* = 7.8, 15.6 Hz, 4-H), 3.82 (2H, q, *J* = 7.0 Hz, O–CH_2–CH_3), 4.11 (1H, dtd, *J* = 2.2, 7.8, 8.0 Hz, 3a-H), 4.14 (1H, br, NH), 6.84 (1H, br t, *J* = 7.2 Hz, 6-H), 6.98 (1H, d, *J* = 7.3 Hz, 8-H), 7.05 (1H, br d, *J* = 6.3 Hz, 5-H), 7.10 (1H, br t, *J* = 7.5 Hz, 7-H). ^{13}C-NMR δ: 13.7 (C-13), 24.4 (C-10), 33.9 (C-4), 43.8 (C-3), 61.1 (C-12), 66.2 (C-3a), 67.8 (C-2), 115.2 (C-8), 121.9 (C-6), 124.9 (C-5), 127.3 (C-7), 128.0 (C-4a), 152.2 (C-8a), 175.10 (C-11).

(2*SR*,3a*SR*)-2-Phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8c) mp 87.5—88.0 °C. MS *m/z*: 236 (M^+, 50.2), 132 (42.2), 131 (100). IR ν_{max}^{KBr} cm^{-1}: 3260, 2840, 1605, 1590, 1480, 1473, 1252, 773, 762, 702. ^{1}H-NMR δ: 2.05—2.38 (2H, m, 3-H), 3.06 (1H, dd, *J* = 1.9, 15.8 Hz, 4-H), 3.28 (1H, dd, *J* = 8.3, 15.8 Hz, 4-H), 3.97 (1H, br, NH), 4.05 (1H, t, *J* = 8.0 Hz, 2-H), 4.24 (1H, m, 3a-H), 6.91 (1H, t, *J* = 7.2 Hz, 6-H), 7.11 (1H, t, *J* = 7.3 Hz, 7-H), 7.17 (1H, br d, *J* = 8.5 Hz, 8-H), 7.25—7.40 (6H, m, Ar-H). ^{13}C-NMR δ: 35.1 (C-4), 42.5 (C-3), 62.6 (C-2), 66.4 (C-3a), 115.0 (C-8), 122.0 (C-6), 124.7 (C-5), 127.0 (d, 2 × C), 127.6 (C-7), 127.7 (d), 128.7 (d, 2 × C), 128.8 (C-4a), 140.6 (s), 152.7 (C-8a). *Anal.* Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85. Found: C, 81.33; H, 6.81; N, 11.87.

2,2-Dimethyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8e(=9e)) Oil. HRMS Calcd for $C_{12}H_{16}N_2$: 188.1315. Found: 188.1317. MS *m/z* 188 (M^+, 40), 173 (8), 133 (18), 132 (43), 131 (100), 130 (30). IR ν_{max}^{film} cm^{-1}: 3260, 2960, 2866, 1607, 1594, 1475, 1246, 759. ^{1}H-NMR δ: 0.97 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.63 (1H, dd, *J* = 8.2, 12.6 Hz, 3-H), 2.01 (1H, dd, *J* = 8.2, 12.6 Hz, 3-H), 2.96 (1H, dd, *J* = 1.7, 15.6 Hz, 4-H), 3.17 (1H, dd, *J* = 8.2, 15.7 Hz, 4-H). 3.81 (1H, br s, NH), 4.09 (1H, qd, *J* = 8.2, 2.1 Hz, 3a-H), 6.83 (1H, dt, *J* = 1.1, 7.2 Hz, 6-H), 6.96 (1H, br d, *J* = 7.6 Hz, 8-H), 7.07 (1H, br d, *J* = 7.1 Hz, 5-H), 7.12 (1H, br t, *J* = 7.8 Hz, 7-H). ^{13}C-NMR δ: 28.6 (C-10), 30.9 (C-11), 34.1 (C-4), 47.8 (C-3), 62.1 (C-2), 66.6 (C-3a), 114.1 (C-8), 121.0 (C-6), 124.9 (C-5), 127.5 (C-7), 127.5 (C-4a), 154.2 (C-8a).

(2*RS*,3a*SR*)-2-Methyl-2-phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8f) Viscous oil. HRMS Calcd for $C_{17}H_{18}N_2$: 250.1471. Found: 250.1509. MS *m/z*: 250 (M^+, 47), 133 (25), 132 (50), 131 (100), 130 (15), 77 (18). IR ν_{max}^{KBr} cm^{-1}: 2953, 1725, 1602, 1591, 1479, 1461, 1263, 762, 701. ^{1}H-NMR δ: 1.25 (3H, s, CH_3), 1.97 (1H, dd, *J* = 7.5, 12.8 Hz, 3-H), 2.63 (1H, dd, *J* = 8.4, 12.8 Hz, 3-H), 3.06 (1H, dd, *J* = 2.4, 15.9 Hz, 4-H), 3.25 (1H, dd, *J* = 8.5, 15.9 Hz, 4-H), 4.1—4.5 (2H, m, 3a-H + NH), 6.83—7.46 (9H, m, Ar-H). ^{13}C-NMR δ: 31.5 (C-10), 34.7 (C-4), 48.4 (C-3), 66.6 (C-3a), 68.1 (C-2), 114.5 (C-8), 121.3 (C-6), 125.0 (C-5), 125.1 (d, 2 × C), 126.9 (C-7), 127.6 (d), 128.6 (d, 2 × C), 130.8 (C-4a), 147.5 (s), 154.3 (C-8a).

(2*SR*,3a*SR*)-2-Methyl-2-phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (9f) Oil. HRMS Calcd for $C_{17}H_{18}N_2$: 250.1471. Found: 250.1509. MS *m/z*: 250 (M^+, 47), 133 (25), 132 (50), 131 (100), 130 (15), 77 (18). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3325, 3012, 2967, 1672, 1607. ^{1}H-NMR δ: 1.56 (3H, s, CH_3), 1.97 (1H, dd, *J* = 10.0, 12.2 Hz, 3-H), 2.31 (1H, dd, *J* = 6.3, 12.2 Hz, 3-H), 2.83 (1H, d, *J* = 15.4 Hz, 4-H), 3.10 (1H, dd, *J* = 7.9, 15.5 Hz, 4-H), 4.0—4.3 (2H, m, 3a-H + NH), 6.75—7.44 (9H, m, Ar-H). ^{13}C-NMR δ: 31.2 (C-10), 32.7 (C-4), 47.6 (C-3), 65.8 (C-3a), 67.5 (C-2), 114.9 (C-8), 121.2 (C-6), 124.8 (C-5), 125.9 (d, 2 × C), 127.4 (C-7), 127.6 (d, 3 × C), 128.6 (C-4a), 148.8 (s), 153.5 (C-8a).

2,2-Diphenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8h(=9h)) mp 136.5—137.5 °C (cyclohexane). HRMS Calcd for $C_{22}H_{20}N_2$: 312.1628. Found: 312.1672. MS *m/z*: 312 (M^+, 23), 182 (6), 132 (59), 131 (100), 105 (22), 77 (22). IR ν_{max}^{KBr} cm^{-1}: 3320, 3021, 2942, 1593, 1472, 1445, 757, 697. ^{1}H-NMR δ: 2.24 (1H, dd, *J* = 9.5, 12.9 Hz, 3-H), 2.87 (1H, d, *J* = 15.4 Hz, 4-H), 3.05 (1H, dd, *J* = 6.6, 12.9 Hz, 3-H), 3.09 (1H, dd, *J* = 8.8, 15.4 Hz, 4-H), 4.28 (1H, m, 3a-H), 4.48 (1H, br s, NH), 6.73—7.43 (14H, m, Ar-H). ^{13}C-NMR δ: 33.2 (C-4), 46.2 (C-3), 66.6 (C-3a), 74.2 (C-2), 115.2 (C-8), 121.4 (C-6), 124.8 (C-5), 125.9 (d), 126.1 (d, 2 × C), 126.9 (d), 127.1 (d, 2 × C), 127.4 (C-7), 127.4 (d, 2 × C), 128.6 (d, 2 × C + 4a), 147.2 (s), 147.7 (s), 153.3 (C-8a). *Anal.* Calcd for $C_{22}H_{20}N_2$: H, 84.58; H, 6.45; M, 8.97. Found: C, 84.66; H, 6.43; N, 8.89.

(2*SR*-3a*SR*)-2-Carbomethoxy-2-phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8i) mp 123.5—124.5 °C (cyclohexane). IR ν_{max}^{KBr} cm^{-1}: 3310, 1720, 1450, 1258, 1190, 760. UV λ_{max}^{EtOH} nm (log ε): 210 (3.31), 237 (3.90), 287 (3.30). MS *m/z*: 294 (M^+, 40.8), 235 (39.5), 132 (100), 131 (76.5), 118 (14.3), 117 (19.3), 104 (31.6), 91 (16.5). ^{1}H-NMR δ: 1.93 (1H, t, *J* = 12.4 Hz, 3-H), 2.91 (1H, d, *J* = 15.4 Hz, 4-H), 3.05 (1H, dd, *J* = 5.6, 12.4 Hz, 3-H), 3.12 (1H, dd, *J* = 7.3, 15.3 Hz, 4-H), 3.73 (3H, s, OCH_3), 4.00 (1H, m, 3a-H), 5.73 (1H, br, NH), 6.80 (1H, m, 6-H), 7.00—7.24 (6H, m, Ar-H), 7.10 (1H, t, *J* = 8.0 Hz, 7-H). ^{13}C-NMR δ: 31.9 (C-4), 43.4 (C-3), 53.1 (C-12), 65.6 (C-3a), 74.3 (C-2), 115.0 (C-8), 121.6 (C-6), 125.0 (C-5), 126.4 (d, 2 × C), 126.6 (C-4a), 127.2 (d), 127.6 (C-7), 127.9 (d, 2 × C), 141.7 (s), 153.8 (C-8a), 174.8 (C-11). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.18; N, 9.54.

(2*RS*-3a*SR*)-2-Carbomethoxy-2-phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (9i) mp 90.0—91.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3226, 1727, 1477, 1450, 729, 701. ^{1}H-NMR δ: 2.52 (1H, dd, *J* = 9.2, 13.1 Hz, 3-H), 3.08 (1H, dd, *J* = 5.7, 13.1 Hz, 3-H), 3.16—3.34 (2H, m, 4-H), 3.23 (3H, s, $COOCH_3$), 4.24 (1H, m, 3a-H), 4.60 (1H, br s, NH), 6.90 (1H, m, 6-H), 7.05—7.46 (8H, m, Ar-H). ^{13}C-NMR δ: 34.9 (C-4), 44.6 (C-3), 52.3 (C-12), 65.8 (C-3a), 74.7 (C-2), 116.1 (C-8), 122.4 (C-6), 124.6 (C-5), 125.9 (d, 2 × C), 127.2 (d), 128.1 (C-7), 128.7 (d, 2 × C), 128.8 (C-4a), 140.2 (s), 151.7 (C-8a), 174.0 (C-11). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.18; N, 9.54.

When cycloaddition was carried out by one-pot procedure, the *Z*-hydrazone **6i** (577 mg, 58.1%), the starting material, the *E*-hydrazone **7i** (184 mg, 18.5%), the cycloadduct **8i** (60 mg, 6.0%) and **9i** (20 mg, 2.0%) were obtained.

One-Pot Cycloaddition of Acetaldehyde 2-Allylphenylhydrazone Generated *in Situ*: General Method A mixture of 2-allylphenylhydrazine (300 mg, 2 mmol), acetaldehyde (90%, 120 mg, 2.4 mmol) and 0.2% sulfuric acid in ethanol (3 ml) was stirred under argon at room temperature for 1 h. After addition of sulfuric acid (0.15 ml) (10% sulfuric acid) and standing for 1 h, the reaction mixture was refluxed for 0.5 h (bath temperature 110 °C). Dilution, basification and extraction of the reaction mixture gave an oily crude product (287 mg). The purified specimen was homogeneous on TLC but was a mixture of stereoisomers, **8b** and **9b** (266 mg, 75% yield) according to ^{1}H-NMR analysis (93 : 7).

Mixture of (2*SR*,3a*SR*)-2-Methyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8b) and (2*RS*,3a*SR*)-Isomer, 9b Oil. HRMS Calcd for $C_{11}H_{14}N_2$: 174.1158. Found: 174.1179. MS *m/z*: 174 (M^+, 64), 132 (35), 131 (100), 130 (40), 117 (19), 103 (14). IR ν_{max}^{film} cm^{-1}: 3246, 2960, 2866, 1606, 1594, 1476, 1259, 764. ^{1}H-NMR for major isomer **8b** δ: 1.16 (3H, d, *J* = 6.4 Hz, CH_3), 1.64—1.92 (2H, m, 3-H), 2.94 (1H, d, *J* = 2.6, 16.0 Hz, 4-H), 3.06 (1H, m,

2-H), 3.20 (1H, dd, J=8.7, 16.0 Hz, 4-H), 3.47 (1H, br s, NH), 4.06 (1H, m, 3a-H), 6.86 (1H, dt, J=1.1, 7.3 Hz, 6-H), 7.00 (1H, br d, J=7.8 Hz, 8-H), 7.06 (1H, br d, J=7.3 Hz, 5-H), 7.14 (1H, m, 7-H). ^{13}C-NMR for major isomer **8b** δ: 18.1 (C-11), 35.3 (C-4), 43.1 (C-3), 54.0 (C-2), 65.7 (C-3a), 114.9 (C-8), 121.8 (C-6), 124.5 (C-5), 127.6 (C-7), 129.1 (C-4a), 152.9 (C-8a). ^{1}H-NMR for minor isomer **9b** δ: 0.97 (d, J=6.6 Hz, CH_3). ^{13}C-NMR for minor isomer **9b** δ: 23.7 (C-11), 33.2 (C-4), 41.0 (C-3), 56.0 (C-2), 66.8 (C-3a), 114.4 (C-8), 121.1 (C-6), 125.0 (C-5), 127.4 (C-7).

When the one-pot reaction was carried out in 60% acetic acid by standing at room temperature for 1 h, then refluxing for 1 h, the product (53% yield) did not include the above minor product but was a mixture of **8b** (major) and the oxidized product (minor), 2-methyl-3a,4-dihydro-3*H*-pyrazolo[1,5-*a*]indole (17%). Signals for the minor product, ^{1}H-NMR δ: 1.98 (s, CH_3), 4.54 (m, 3a-H). ^{13}C-NMR δ: 15.9 (C-11), 37.5 (C-4), 44.37 (C-3), 62.0 (C-3a), 117.8 (C-8), 124.1 (C-6), 125.0 (C-5), 127.8 (C-7).

(2*RS*,3a*SR*)-2-Carboethoxy-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (8d) Gummy material. HRMS Calcd for $C_{13}H_{16}N_2O_2$: 232.1213. Found: 232.1246. MS m/z: 232 (M^+, 34), 159 (29), 132 (100), 131 (41), 130 (37), 117 (23). IR ν_{max}^{film} cm^{-1}: 3301, 2979, 2940, 1733, 1607, 1595, 1475, 1205, 760. ^{1}H-NMR δ: 1.27 (3H, t, J=7.1 Hz, CH_2–C$\underline{H}_3$), 2.00 (1H, ddd, J=8.3, 10.1, 12.9 Hz, 3-H), 2.24 (1H, ddd, J=5.4, 8.1, 12.9 Hz, 3-H), 2.98 (1H, d, J=15.6 Hz, 4-H), 3.18 (1H, dd, J=7.6, 15.6 Hz, 4-H), 3.66 (1H, br m, 2-H), 3.91 (1H, m, 3a-H), 4.21 (2H, q, J=7.2 Hz, OCH_2–CH_3), 4.75 (1H, br s, NH), 6.89 (1H, dt, J=1.1, 7.3 Hz, 6-H), 7.01 (1H, br d, J=7.6 Hz, 8-H), 7.10 (1H, br d, J=8.1 Hz, 5-H), 7.16 (1H, br t, J=7.9 Hz, 7-H). ^{13}C-NMR δ: 14.1 (C-13), 33.5 (C-4), 38.3 (C-3), 59.7 (C-2), 61.4 (C-12), 64.8 (C-3a), 114.6 (C-8), 122.3 (C-6), 125.0 (C-5), 127.6 (C-4a), 127.7 (C-7), 152.7 (C-8a), 173.5 (C-11).

2-Phenyl-3a,4-dihydro-3*H*-pyrazolo[1,5-*a*]indole (10) a) Swern Oxidation[10] of **8c**: A solution of dimethylsulfoxide (DMSO, 0.32 ml, 45 mmol) and dry dichloromethane (0.5 ml) was introduced into a mixture of dry dichloromethane (3 ml) and oxalyl chloride (0.20 ml, 23 mmol) at −60 °C for 2 min, then the mixture was kept at −60 °C for 3 min. A solution of the cycloadduct **8c** (473 mg, 2 mmol) in dry dichloromethane (0.5 ml) was added to this reagent for 3 min and after 10 min triethylamine (1.40 ml) was added. The reaction mixture was left at room temperature for 25 min then quenched with water (3 ml). The crude product was chromatographed and the crystalline product (248 mg, 53% yield) was recrystallized from dichloromethane–cyclohexane to give **10** (231 mg, 49% yield): mp 95.0—96.0 °C (lit.,[4b] mp 95.0—95.5 °C).

b) Oxidation of 12 with Periodic Acid: A solution of the aminoalcohol **12** (100 mg, 0.38 mmol) in a mixture of methanol (5 ml) and water (2 ml) was treated with periodic acid dihydrate (81 mg, 0.36 mmol) at 5 °C for 30 min. The reaction mixture was neutralized with 1N barium hydroxide and filtered to remove the precipitate. The filtrate was evaporated and the residue, after dilution with water (10 ml), was extracted with ether (10 ml + 5 ml × 2). The crude product was purified by column chromatography to give **10** (56.5 mg, 64.2% yield), mp 94.5—95.5 °C.

(2*SR*,3a*SR*)-2-Hydroxymethyl-2-phenyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (12) A solution of the ester **8i** (500 mg, 1.7 mmol) in dry ether (20 ml) was added to a suspension of lithium aluminum hydride (60 mg, 1.6 mmol) in dry ether (10 ml) and the resulting solution was stirred at room temperature for 3 h. Water (0.2 ml) was added to decompose the reagent and the precipitate was removed by filtration and washed well with ether. The filtrate and washings were combined and evaporated to give **12** (443 mg, 97.9%): mp 148.0—148.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3670, 1598, 1475, 1258, 1041, 762, 698. ^{1}H-NMR δ: 1.92 (1H, dd, J=9.7, 12.4 Hz, 3-H), 2.48 (1H, dd, J=6.8, 12.4 Hz, 3-H), 2.84 (1H, d, J=15.6 Hz, 4-H), 3.08 (1H, dd, J=7.8, 15.6 Hz, 4-H), 3.63 (2H, s, C$\underline{H}_2$OH), 4.13 (1H, m, 3a-H), 6.73 (1H, m, 6-H), 6.95 (1H, d, J=7.0 Hz, 5-H), 7.03 (1H, t, J=8.0 Hz, 7-H), 7.06—7.22 (5H, m, Ar-H), 7.45 (2H, m, Ar-H). ^{13}C-NMR δ: 32.9 (C-4), 43.2 (C-3), 66.4 (C-3a), 70.4 (C-11), 72.0 (C-2), 115.0 (d), 121.4 (d), 124.9 (d), 126.5 (d), 126.9 (d, 2 × C), 127.2 (C-4a), 127.4 (C-7), 127.8 (d, 2 × C), 145.0 (s), 153.3 (C-8a). *Anal.* Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.52; H, 6.77; N, 10.49.

2-Carboethoxy-2-methyl-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]indole (13a) A mixture of **8g** and **9g** (33 mg, 0.13 mmol), triethylamine (0.05 ml, 0.35 mmol), and palladium chloride (30 mg, 0.17 mmol) in dry methanol (2.0 ml) was stirred in dry nitrogen for 8.5 h.[12] The brown solution became black within 1 h. The reaction mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was treated with aqueous sodium carbonate, then extracted with ether three times. The crude product (48 mg) was separated by column chromatography to give **13a** (26 mg, 79% yield) and the starting material **8g** (7 mg). **13a**, oil. HRMS Calcd for $C_{14}H_{16}N_2O_2$: 244.1210; Found: 244.1218. MS m/z: 244 (M^+, 95.5), 171 (100), 170 (39.3), 156 (23.2), 154 (14.3), 144 (14.3), 130 (34.8), 129 (53.5). UV λ_{max}^{EtOH} nm (log ε): 276 (3.73), 230 (4.23); $\lambda_{max}^{EtOH+HCl}$ nm (log ε): 277 (3.73), 230 (4.23). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3245, 1735, 1615, 1552, 1452, 1293, 1019, 920, 861. ^{1}H-NMR δ: 1.28 (3H, t, J=7.0 Hz, CH_2–C$\underline{H}_3$), 1.49 (3H, s, CH_3), 3.00 (1H, d, J=15.6 Hz, 3-H), 3.43 (1H, d, J=15.6 Hz, 3-H), 4.25 (2H, q, J=7.0 Hz, O–C$\underline{H}_2$–CH_3), 5.54 (1H, br, NH), 6.14 (1H, s, 4-H), 7.01 (1H, dt, J=1.22, 7.4 Hz, 6-H), 7.12 (1H, dt, J=0.9, 7.5 Hz, 7-H), 7.31 (1H, d, J=8.1 Hz, 8-H), 7.50 (1H, d, J=7.5 Hz, 5-H). ^{13}C-NMR δ: 14.1 (C-13), 23.4 (C-10), 37.9 (C-3), 62.0 (C-12), 72.3 (C-2), 92.0 (C-4), 108.6 (C-8), 119.1 (C-6), 120.6 (C-5), 121.0 (C-7), 130.1 (C-3a), 131.1 (C-4a), 137.1 (C-8a), 172.9 (C-11).

2-Carboxymethyl-2-phenyl-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]indole (13b) **8i** (500 mg, 1.7 mmol) and 5% palladium on charcoal (120 mg) were added to anhydrous xylene (50 ml), and the resulting solution was refluxed for 18.5 h (bath temperature 155 °C) until the starting material had disappeared. The catalyst was removed by filtration *via* a Celite pad and the Celite was washed with benzene. The filtrate and washing were combined and evaporated. The residue (651 mg) was purified by column chromatography to give crystalline **13b** (447 mg, 90%), mp 137.5—138.5 °C (cyclohexane). HRMS Calcd for $C_{18}H_{16}N_2O_2$: 292.1257. Found: 292.1262. MS m/z: 292 (M^+, 43), 233 (100), 206 (13), 130 (34), 129 (12), 116 (13), 104 (27), 102 (16), 77 (30). IR ν_{max}^{KBr} cm^{-1}: 3210, 1738, 1282, 1245, 746. UV $\lambda_{max}^{ethanol}$ nm (log ε): 223 (4.60), 275 (4.14). ^{1}H-NMR δ: 3.56 (1H, d, J=15.6 Hz, 3-H), 3.17 (3H, s, CH_3), 3.92 (1H, d, J=15.6 Hz, 3-H), 5.55 (1H, br s, NH), 6.10 (1H, s, 4-H), 5.98 (1H, dt, J=0.9, 7.4 Hz, 6-H), 7.13 (1H, dt, J=1.2, 7.5 Hz, 7-H), 7.25—7.35 (3H, m, Ar-H), 7.40 (1H, d, J=7.0 Hz, 8-H), 7.44 (1H, J=7.3 Hz, 5-H), 7.60 (2H, m, Ar-H). ^{13}C-NMR δ: 38.0 (C-3), 53.3 (C-12), 78.2 (C-2), 91.9 (C-4), 108.6 (C-8), 119.2 (C-6), 120.6 (C-5), 121.1 (C-7), 126.1 (d, 2 × C), 128.3 (s), 128.5 (d), 128.6 (d, 2 × C), 130.0 (s), 130.9 (s), 136.9 (s), 138.1 (s), 172.07 (C-11). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.08; H, 5.51; N, 9.59.

Reduction of 13a and 13b with Sodium Cyanoborohydride Compound **13a** (22 mg) and sodium cyanoborohydride (90%, 45 mg) were dissolved in methanol (2 ml) containing a few drops of methyl orange. Methanolic 2N hydrochloric acid was gradually dropped in until the red color persisted. The reaction mixture was left at room temperature overnight then diluted with aqueous sodium carbonate and extracted with ether. Column chromatography of the crude product (17 mg) gave **8g** (6 mg, 27%) and **9g** (4 mg, 18%). When **13b** (292 mg) was reduced with sodium cyanoborohydride (300 mg) in the same manner, the crystallization of the crude product gave **8i** (220 mg, 75% yield). The mother liquor was flash-chromatographed to give **8i** (30 mg, total 250 mg, 85% yield). The presence of **9i** as an impurity was detected from the ^{13}C-NMR spectrum (signals at δ: 34.9, 44.6, 52.3, 65.8, 74.7, 116.1, 122.4, 124.6, 125.9, 128.7).

Reduction of 13a with Sodium Cyanoborodeuteride Compound **13a** (300 mg, 1.2 mmol) was dissolved in a mixture of AcOD (98%, 3 ml) and deuterium oxide (99.8%, 1.5 ml) and stirred at room temperature for 10 min. Then sodium cyanoborodeuteride (98% D, 300 mg) was added. After 30 min, further reagent (150 mg, total 450 mg, 6.8 mmol) was added and the reaction was continued for 1.5 h. After addition of deuterium oxide (3.5 ml) and basification with sodium carbonate, the solution was diluted with water and extracted with ether three times. The crude product (329 mg) showed a series of spots on a TLC plate and was chromatographed twice with dichloromethane–ethyl acetate (97:3). Among two major products the polar isomer **14** (84 mg, 27% yield) was isolated as a pale yellow syrup. The main product was contaminated with by-products and was difficult to isolate in pure form. The above yield was the best among many attempts.

(2*RS*,3a*SR*)-(3a,4,4-Trideuterio)-2-carboethoxy-2-methyl-2,3,3a,4-tetrahydro-1*H*-pyrazolo[1,5-*a*]indole (14) MS m/z: 249 (M^+, 58), 176 (53), 158 (4), 149 (9), 135 (50), 134 (83), 133 (100), 132 (27), 119 (13). ^{1}H-NMR δ: 0.98 (3H, t, J=7.1 Hz, CH_2–C$\underline{H}_3$), 1.45 (3H, s, CH_3), 1.99 (1H, d, J=12.9 Hz, 3-H), 2.49 (1H, d, J=12.9 Hz, 3-H), 3.81 (2H, q, J=7.1 Hz, O–C$\underline{H}_2$–CH_3), 4.07 (1H, br s, NH), 6.83 (1H, dt, J=1.3, 7.2 Hz, 6-H), 6.96—7.14 (3H, m, Ar-H). ^{13}C-NMR δ: 13.7 (C-13), 24.3 (C-9), 33.2 (quintet, C-4), 43.6 (C-3), 61.0 (C-12), 65.6 (t, C-3a), 67.8 (C-2), 115.2 (C-8), 121.8 (C-6), 124.7 (C-5), 127.2 (C-7), 127.9 (C-4a), 152.3 (C-8a), 175.1 (C-11).

Exchange of 4-H with Deuterium A solution of **13a** (49.5 mg, 0.2 mmol), AcOD (98%, 0.5 ml) and deuterium oxide (99.96%, 0.25 ml) was stirred at room temperature for 15 min. Dilution with deuterium oxide (1 ml), basification with excess sodium carbonate, and extraction with ether gave **15** (98% yield). It was found that 95% of 4-H was exchanged with deuterium according to ^{1}H-NMR analysis. During purification by

column chromatography more than 50% of 4-D was replaced with hydrogen.

(4-Deuterio)-2-carboethoxy-2-methyl-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]-indole (15) ^{1}H-NMR δ: 1.28 (3H, t, J=7.2 Hz, CH_2–CH_3), 1.47 (3H, s, CH_3), 2.99 (1H, d, J=15.6 Hz, 3-H), 3.40 (1H, d, J=15.6 Hz, 3-H), 4.25 (2H, q, J=7.2 Hz, O–CH_2–CH_3), 5.49 (1H, br s, NH), 7.02—7.21 (2H, Ar-H), 7.31 (1H, d, J=8.1 Hz, 8-H), 7.50 (1H, d, J=7.6 Hz, 5-H). ^{13}C-NMR δ: 14.0 (C-13), 23.4 (C-10), 37.7 (C-3), 62.0 (C-12), 72.3 (C-2), 108.6 (C-8), 119.0 (C-6), 120.5 (C-5), 121.0 (C-7), 129.9 (C-3a), 131.0 (C-4a), 137.1 (C-8a), 172.9 (C-11). The signal of C-4 was not seen.

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