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Fischer Indolization of 2-Sulfonyloxyphenylhydrazones: A New and Practical Approach for Preparing 7-Oxygenated Indoles and Application to the First Synthesis of Eudistomidin-A. (Fischer Indolization and Its Related Compounds. Part 28[1,2])

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Abstract: An efficient method for synthesis of 7-oxygenated indoles was established by Fischer indolization of the phenylhydrazones (**10**) with a sulfonyloxy group at the *ortho*-position. This method was applied to the first synthesis of the calmodulin antagonist eudistomidin-A (**2**).

There are many biologically active indole alkaloids with an oxygen function (a methoxy group in most cases) at the 7-position of the indole nucleus such as mitomycin-C[3a], PDE,[3b] aspidospermine,[3c] duocarmycin C_2,[3d] discorhabdin C[3e] *etc.* (Fig. 1). 7-Oxygenated indole (**1**) is the mother skeleton and a

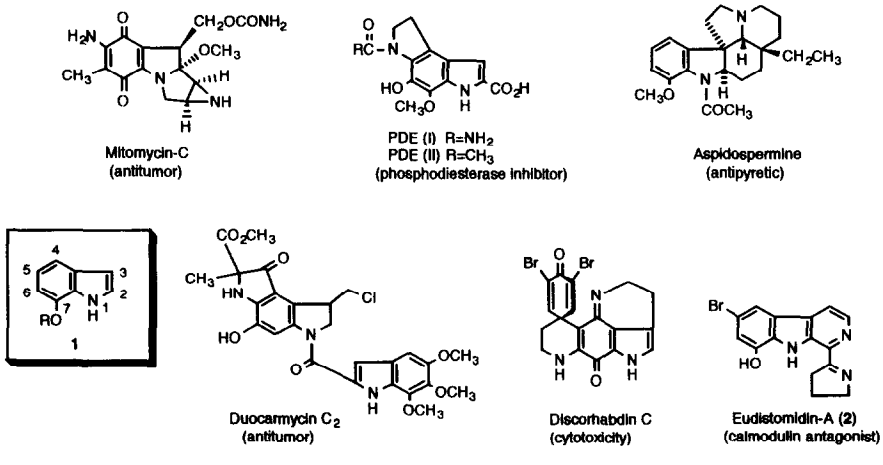

Fig. 1 Indole Alkaloids with an Oxygen Function at the 7-Position of the Indole Nucleus

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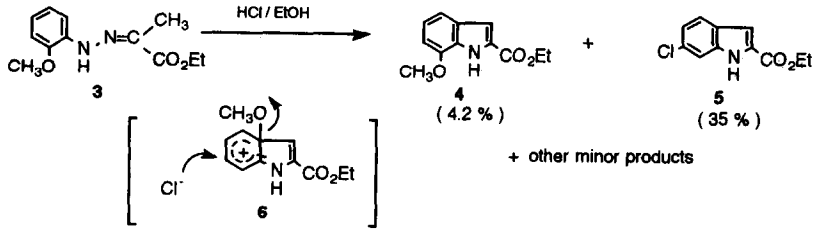
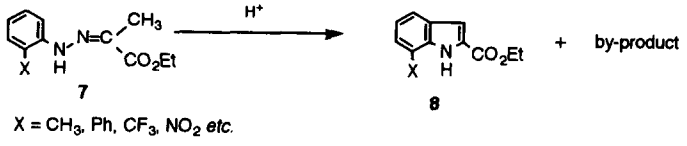
starting material for synthesis of these compounds in many cases. However, it is not so easy to obtain **1**. Representative methods for obtaining the indole nucleus are Reissert reaction, [4] Batcho-Leimgruber reaction,[5] Hemetsberger-Knittel reaction,[6] and Fischer indole synthesis[7] (Fischer indolization). Fischer indolization, which requires 2-methoxyphenylhydrazone as the starting material, seems to be most convenient and effective for the present purpose, if cyclization would be restricted to the unoccupied site. Fischer indolization[8] of ethyl pyruvate 2-(2-methoxyphenyl)hydrazone (**3**), however, resulted in the formation of ethyl 6-chloroindole-2-carboxylate (**5**) as the main but abnormal product along with the normal and expected product, ethyl 7-methoxyindole-2-carboxylate (**4**), as a minor component. This was due to cyclization toward the position occupied by the methoxy group through the intermediate **6** (Scheme 1).



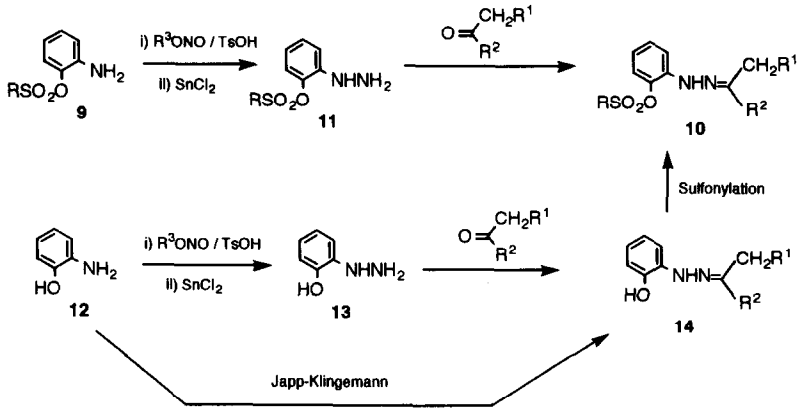
Scheme 1

We studied[9] the Fischer indolization of variously *ortho*-substituted phenylhydrazones (**7**) to examine the effect of the *ortho*-substituent in cyclization (Scheme 2). This experiment showed that phenylhydrazones with *ortho*-substituents which were stronger electron donors cyclized more toward the position occupied with the substituent to yield abnomal products, whereas those with more electron-attractive *ortho*-substituents cyclized more toward the unoccupied position to yield the normal 7-substituted indole. This result suggested that phenylhydrazones (**7**) with electron-attractive oxygenated substituents at the *ortho*-position would give 7-oxygenated indoles from which 7-methoxyindoles could be obtained easily, much more than from those with a methoxy group (**3**).



Scheme 2

As a functionality X in **7**, we selected the sulfonyloxy group which is a strong electron-attractive group and its removal yields the corresponding phenol. As sulfonyloxy groups, *p*-substituted benzenesulfonyloxy, methanesulfonyloxy and trifluoromethanesulfonyloxy groups were used. Starting 2-sulfonyloxyphenylhydrazones (**10**) were prepared by Japp-Klingemann reaction or by reaction of ketone with the corresponding 2-sulfonyloxyphenylhydrazine (**11**) or with 2-hydroxyphenylhydrazine (**13**), followed by sulfonylation (Scheme 3).

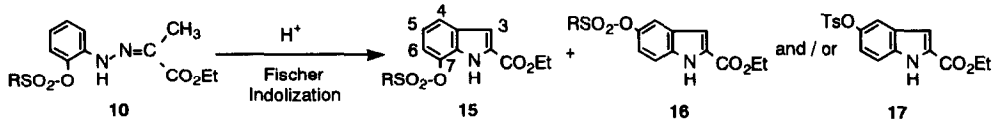


Scheme 3 Preparation of 2-Sulfonyloxyphenylhydrazones

Fischer Indolization

The Fischer indolization of **10** was carried out with polyphosphoric acid (PPA) and *p*-toluenesulfonic acid (TsOH).[10] The results are summarized in Table 1. The total yields of indolic products were ranged from 46 to 91%. In Fischer indolization, two or three kinds of the products were formed; 7-sulfonyloxyindole (**15**) as normal product, 5-sulfonyloxyindole (**16**) and/or 5-(*p*-toluenesulfonyloxy)indole (**17**) as abnormal

Table 1 The Fischer Indolization of Ethyl Pyruvate 2-(2-Sulfonyloxyphenyl)hydrazone



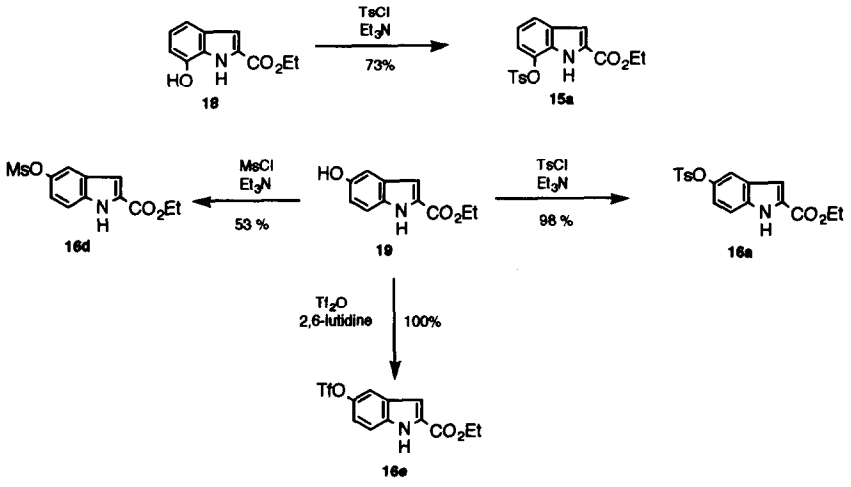
10 15 16 17

Run	10 (R =)	H^+	Conditions Temp.	Time	Yield (%) Total	15	16	17	Ratio 15 / 16+17
1		PPA	85 °C,	30 min	47	37	10	---	3.7
2	a (= Ts)	TsOH / benzene	reflux,	13.5 h	72	54	18	---	3.0
3		PPA	70 °C,	2.5 h	58	45	13	---	3.5
4	b	TsOH / benzene	reflux,	10.5 h	53	38	8	7	2.5
5		PPA	80 °C,	4 h	50	39	11	---	3.5
6	$-CH_3$ (= Ms)	PPA	50 °C,	2 h	46	39	7	---	5.6
7	d	TsOH / benzene	reflux,	3 h	91	61	11	19	2.0
8	$-CF_3$ (= Tf)	PPA	80 °C,	1 h	60	53	7	---	7.6
9	e	TsOH / toluene	reflux,	25 h	82	73	9	---	8.1

products. The mechanisms of formation of **16** and **17** are described later. In all cases, the expected normal 7-sulfonyloxyindole (**15**) was the major product and was easily isolated by column chromatography. As an acid catalyst, TsOH in benzene gave generally better total yields than PPA, although the reaction with TsOH /benzene was slower. With regard to the ratio of **15** / **16**+**17**, PPA was better than TsOH in benzene, but the difference was not big. TsOH in benzene was therefore a better catalyst than PPA with regard to yield and with ease of handling. Other catalysts such as HCl/EtOH and $ZnCl_2$/AcOH gave poor results. Compared with the Fischer indolization of *o*-methoxyphenylhydrazone, *o*-sulfonyloxy group causes the reaction to occur more favorably in the normal direction. Although the substituent effect on the benzene nucleus of **10** for the direction of cyclization was negligible (Runs 1-5), it was apparent from the results with mesyl (Runs 6 and 7) and trifluoromethanesulfonyl (Runs 8 and 9) groups that the more electron-attractive sulfonyl group resulted in a higher ratio of **15**.

Mechanism of the Formation of Abnormal Products

To confirm the structures of the products, ethyl 7-tosyloxyindole-2-carboxylate (**15a**) and ethyl 5-mesyloxy-(**16d**), 5-trifluoromethanesulfonyloxy-(**16e**), and 5-tosyloxy-(**16a**) indole-2-carboxylates were prepared from known corresponding hydroxyindoles (**18** and **19**) by *O*-sulfonylation (Scheme 4). The Fischer products, **15a**, **16a**, **16d** and **16e** were identified with the samples prepared above.

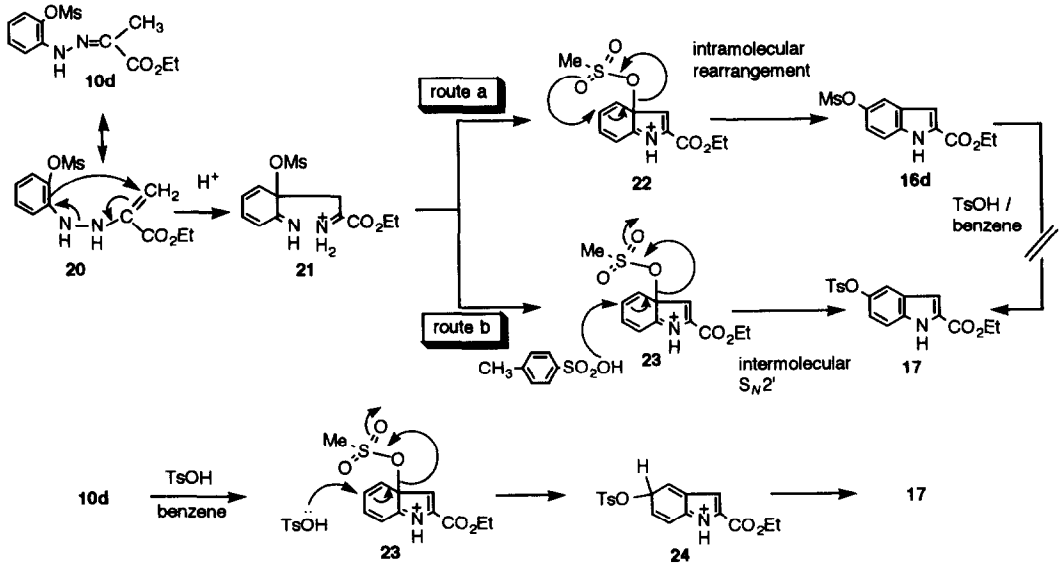


Scheme 4

The nomal product, ethyl 7-sulfonyloxyindole-2-carboxylate (**15**), was produced by cyclization at the unoccupied *ortho*-position by the usual Fischer indolization mechanism. The abnormal products (**16** and **17**) should be produced by cyclization at the substituted *ortho*-position by abnormal Fischer indolization similarly to the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)hydrazone (**3**),[8] because **16** and **17** were not produced by direct treatment of the normal product (**15**) under Fischer indolization conditions. The proposed mechanism is shown for **10d** in Scheme 5.

At first we investigated the mechanism of formation of ethyl 5-mesyloxyindole-2-carboxylate (**16d**). The hydrazone (**10d**) was cyclized in a [3, 3]sigmatropic manner to give the diimine intermediate (**21**). The

intermediate (**21**) cyclized to the cation intermediate (**22**), in which the mesyloxy group rearranged on the indolic 5-position to give ethyl 5-mesyloxyindole-2-carboxylate (**16d**) in route **a**. A similar rearragement was reported in the synthesis of 7-tosyloxybenzofuran derivatives.[11] On the other hand, the cation (**23**) in route **b** was attacked intermolecularly (S_N2') at the same 5-position by TsOH with elimination of the mesyloxy group to give ethyl 5-tosyloxyindole-2-carboxylate (**17**).



Scheme 5

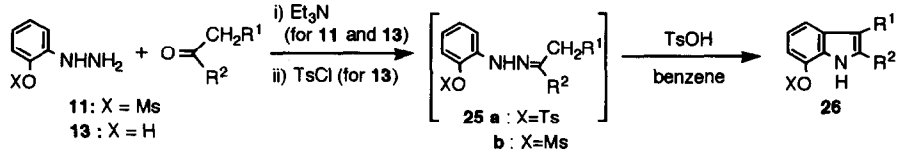
It seemed strange that similar intermediates (**23** and **6**), which were derived from the hydrazones (**10d**) and **3**, respectively, gave different products, the 5-tosyloxyindole (**17**) or the 6-chloroindole (**5**). We considered this to be due to the differences in leaving ability of the mesyloxy and methoxy groups. The nucleophilic chloro anion attacked the cationic intermediate (**6**) before elimination of the methoxy group in **6**, whereas the mesyloxy group which has good leaving ability was substituted in S_N2' with weakly nucleophilic TsOH on the cationic intermediate (**23**). This difference would give rise to the different products (**17** and **5**). In addition the treatment of the 5-mesyloxyindole (**16d**) with TsOH/benzene did not give 7-tosyloxyindole (**17**) but resulted in recovery of the starting indole (**16d**).

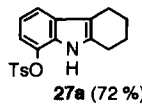
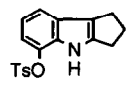
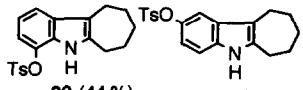
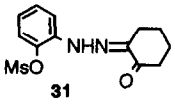
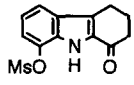
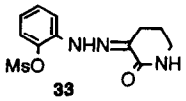
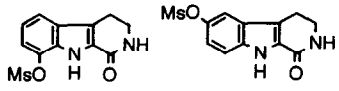
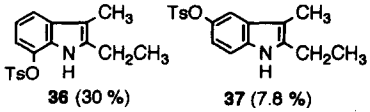
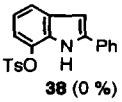
Extension to Various Hydrazones

The above Fischer indolization was extended to hydrazones prepared from ketones other than ethyl pyruvate. The hydrazones (**25**) were prepared from a hydrazine and a ketone, and were isolated. In cases where the hydrazone (**25**) was too unstable to isolate, the reaction was carried out just after mixing 2-mesyloxy-(**11**) or 2-hydroxy-(**13**)phenyhydrazine and a ketone followed by sulfonylation (in case of **13**). Tosyloxy and mesyloxy groups were used as 2-sulfonyloxy group in the hydrazones (**25**) from the point of view of practical use, although the use of trifluoromethanesulfonyloxy group could give better ratio of the normal product (**26**) as shown in the result of Table 1. The Fischer indolization reaction were carried out

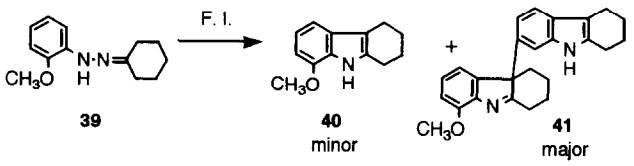
using TsOH in benzene. The results are summarized in Table 2. Total yields were generally moderate, and in contrast to the Fischer indolization of the hydrazone from ethyl pyruvate, most reactions gave only the expected normal 7-tosyloxy indole and no abnormal rearranged by-product.

Table 2 Fischer Indolization of *o*-Sulfonyloxyphenylhydrazone of Various Ketones



Run	Starting material	Conditions Temp.	Time	Normal product	By-product
1) Cyclic ketones					
1	**13** + 	reflux	50 min	 **27a** (72 %)	0 %
2	**11** + 	reflux	2 h	**27b** (36 %)	0 %
3	**13** + 	reflux	2.5 h	 **28** (37 %)	0 %
4	**13** + 	reflux	1 h	 **29** (44 %)	**30** (7.3 %)
5	 **31**	reflux	2 h	 **32** (64 %)	0 %
6	 **33**	reflux	18 h	 **34** (70 %)	**35** (3.4 %)
2) Acyclic ketones					
7	**13** + $(CH_3CH_2)_2CO$	reflux	20 min	 **36** (30 %)	**37** (7.8 %)
8	**13** + CH_3COPh	reflux	2 h	 **38** (0 %)	——

Fischer indolization of cyclohexanone 2-methoxyphenylhydrazone (**39**) was reported[12] to give small amounts of normal 8-methoxycarbazole (**40**) with large amounts of abnormal product. The structure of this abnormal product was estimated[10] to be the dimeric indole (**41**) (Scheme 6).



Scheme 6

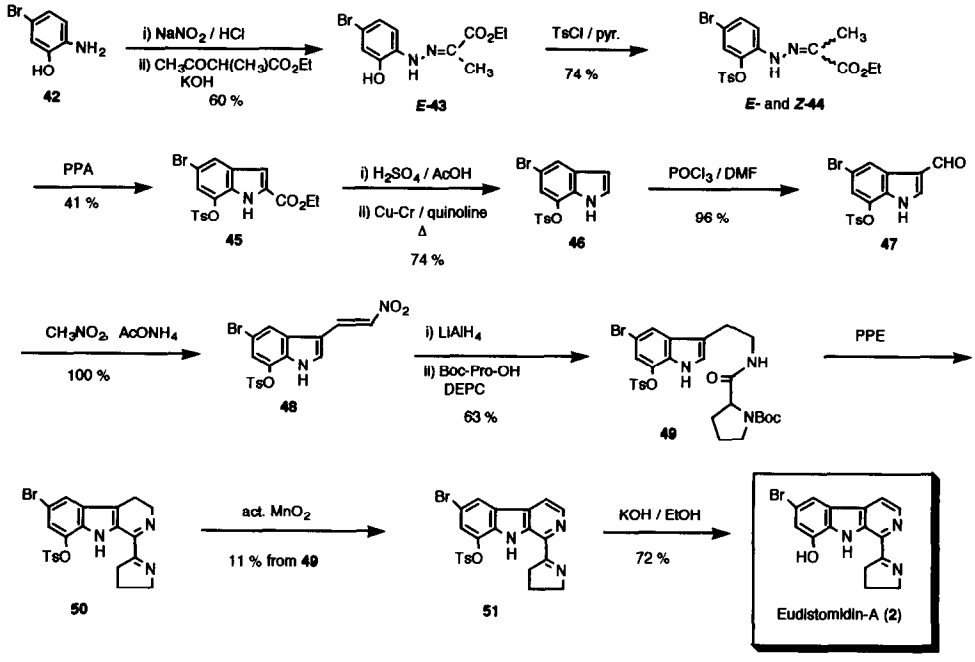
Recently, Heathcock[13] reported a new approach for preparing 7-oxygenated indoles in which restriction of the conformation in Fischer indolization reaction was effective to control the direction of cyclization. The results of the present study indicated that our Fischer indolization method would be practically covenient and useful for synthesizing 7-oxygenated indoles.

Total Synthesis of Eudistomidin-A (2)

As a practical application of the present Fischer indolization method for preparing 7-oxygenated indole, biologically active eudistomidin-A (**2**) was synthesized as follows.

Eudistomidin-A (**2**) is an alkaloid isolated[14] from Okinawan tunicate, *Eudistoma glaucus*, and has been reported to have a calmodulin antagonistic effect. The alkaloid is a β-carboline with 6-bromo and 8-hydroxy (5- and 7-positions in indole-numbering) groups and had not been synthesized previously. The synthetic scheme is shown in Scheme 7.

To synthesize **2**, 5-bromo-7-oxygenated indole (**46**) was required as the starting material. Fischer indolization of cyclohexanone 4-bromo-2-methoxyphenylhydrazone was reported[15] to give the corresponding normal product, 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydrocarbazole in a moderate yield, whereas it was known[8, 12, 13, 16] that 2-methoxyphenylhydrazones generally gave normal 7-methoxyindoles in unsatisfactory yields. Thus, we applied present Fischer indolization method to the synthesis of **46**. The subsequent steps were performed essentially according to Hino's method.[17] The known 2-amino-5-bromophenol[18] (**42**) was converted into ethyl pyruvate 2-(4-bromo-2-tosyloxyphenyl)hydrazone (**44**). Fischer indolization of the hydrazone (**44**) was successfully carried out with PPA to yield the expected ethyl 5-bromo-7-tosyloxyindole-2-carboxylate (**45**) as the sole isolable product (41% yield). The hydrolysis of **45** under acidic conditions followed by decarboxylation gave 5-bromo-7-tosyloxyindole (**46**). Vilsmeier-Haack formylation followed by the treatment with nitromethane gave the nitrovinylindole (**48**), which was converted into the *N*-protected amide (**49**) by reduction with lithium aluminum hydride, followed by the protection with a Boc group. The Bischler-Napieralski reaction of **49** with polyphosphoric ester (PPE) and subsequent dehydrogenation with active manganese dioxide gave the β-carboline (**51**), although in low yield. The final deprotection step of **51** with potassium hydroxide in ethanol gave the target product (**2**), mp 265-280 °C, which was identical to the natural product, mp 260-270 °C,[19] in all respects.



Scheme 7 Total Synthesis of Eudistomidin-A

Further application of this strategy to the synthesis of natural products will be published elsewhere.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanaco) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrometer. ^{1}H-NMR spectra were measured on a Hitachi R-24B (60 MHz),unless otherwise stated and JEOL EX-400 (400 MHz). Deuteriochloroform was used as the solvent with tetramethylsilane as an internal reference, unless otherwise stated. The assignments of NH signals were confirmed by disappearance of the signals after addition of deuterium oxide. Mass spectra (MS) were measured on JEOL JMS-01-SG-2, JEOL JMS-D300, and JEOL JMS-DX303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70-230 mesh ASTM, Merck, unless otherwise stated), and for thin layer chromatography (TLC), Silica gel $60F_{254}$(Merck) were used. All identifications of products were done by analysis of MS, IR, and especially NMR spectra. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; br, broad; Ar, aromatic; BP, base peak.

General Procedure for Preparation of Ethyl Pyruvate 2-(2-Sulfonyloxyphenyl)hydrazones (10)

1-1) 2-Hydroxyphenylhydrazine *p*-Toluenesulfonate (13)

To a solution of 2-aminophenol hydrochloride (**12**) (2.99 g, 20 mmol) in EtOH (15 mL) was added a solution of isoamyl nitrite (3.0 mL, 22 mmol) in EtOH (10 mL) under ice-cooling for preparing of the

diazonium salt. This solution of diazonium salt was added to a mixture of tin (II) chloride (7.54 g, 40 mmol), *p*-toluenesulfonic acid monohydrate (3.84 g, 20 mmol) and EtOH under ice-cooling. The reaction mixture was stirred for 30 min at the same temperature and then ether (50 mL) was added to the mixture. The resulting precipitates were taken by filtration and washed with ether to afford colorless plates (5.27 g, 89%), mp 154-156 °C (dec.), which were recrystallized from EtOH-hexane. *Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C, 52.36; H, 5.37; N, 9.42. IRν_{max}cm^{-1} (Nujol): 3290 and 3100 (NH and OH). NMR (DMSO-d_6) δ: 2.23 (3H, s, Ar-CH_3), 6.54-7.69 (9H, m, Ar-H x 8, NH or OH), 9.60 (4H, br s, NH and OH), MS *m/z* : 124 (free base, 9.8%), 172 (BP).

1-2) Condensation of Hydrazine•TsOH (13) with Ethyl Pyruvate, Followed by Sulfonylation (One-pot Reaction)

To a suspension of the hydrazine•TsOH (**13**) (1 eq) in CH_2Cl_2 was added Et_3N (1.5 eq) and ethyl pyruvate (1.1 eq) under ice-cooling. To this mixture was added Et_3N (1.5 eq) and a solution of sulfonyl chloride (1.1 eq) in CH_2Cl_2 under ice-cooling, and the whole was stirred for 30 min at the same temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% HCl, sat. $NaHCO_3$, and brine successively, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crude residue was purified with column chromatography and recrystallized to afford the hydrazones [(***E***)-and/or (***Z***)-**10**].

2-1) Preparation of Ethyl Pyruvate (*Z*)-2-(2-Hydroxyphenyl)hydrazone (14) from 2-Aminophenol (12) by Japp-Klingemann Reaction

To a solution of 2-aminophenol (**12**) (1.028 g, 9.42 mmol) in conc. HCl (3.74 mL, 37.6 mmol) and water (10 mL) was added dropwise a solution of sodium nitrite (0.796 g, 11.4 mmol) in water (10 mL) under ice-cooling. The resulting diazonium salt was added dropwise to a solution of ethyl α-methylacetoacetate (1.34 mL, 9.48 mmol) and 50% KOH aq. in EtOH (10 mL) at 0-5 °C. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with 10% HCl, sat. $NaHCO_3$, and brine successively, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a reddish brown oil (1.815 g). The crude product was chromatographed over silica gel using ethyl acetate-hexane (1:5) to give pale yellow needles (1.100 g, 53%), mp 131-132 °C, which were recrystallized from benzene-hexane. *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.38; N, 12.58. IRν_{max}cm^{-1} (Nujol): 3290 (NH), 1695 (CO). NMR ($CDCl_3$) δ: 1.29 (3H, t, *J*=7 Hz, $CH_2\underline{CH_3}$), 2.00 (3H, s, =C-CH_3), 4.20 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 6.70-6.85 (4H, m, Ar-H), 7.88 (1H, br s, NH), 9.92 (1H, br s, OH). MS *m/z* : 222 (M+, 61%), 108(BP).

2-2) General Procedure for Sulfonylation of 2-Hydroxyphenylhydrazone (14)

To a solution of 2-hydroxyphenylhydrazone (**14**) (1eq) in pyridine or 2, 6-lutidine was added sulfonyl chloride (2 eq) or trifluoromethanesulfonic anhydride (Tf_2O) (1.5 eq) and the whole was stirred at room temperature to 80 °C for 1-6 h. The reaction mixture was poured into water and extracted with ether or ethyl acetate. The organic layer was washed with 10% $CuSO_4$ aq. and brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The crude residue was purified with columnn chromatography and recrystallized to afford the hydrazones [(***E***)-and/or (***Z***)-**10**].

(*E*)-Ethyl Pyruvate 2-[2-(*p*-Toluenesulfonyloxy)phenylhydrazone] [(*E*)-10a]

Yield: 89%. Yellow prisms, mp 82.5-84 °C (ether). *Anal.* Calcd for $C_{18}H_{20}N_2O_5S$: C, 57.43; H, 5.36; N, 7.44. Found: C, 57.40; H, 5.37; N, 7.42. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1695 (CO). NMR ($CDCl_3$) δ:

1.35 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.01 (3H, s, =C-CH_3), 2.42 (3H, s, Ar-CH_3), 4.28 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.70-7.90 (8H, m, Ar-H), 8.05 (1H, br s, NH). MS *m/z*: 376 (M^+, 20%), 221(BP).

(*Z*)-Ethyl Pyruvate 2-[2-(*p*-Toluenesulfonyloxy)phenylhydrazone] [(*Z*)-10a]

Yield: 6.3%. Yellow prisms, mp 127-130 °C (benzene-hexane). *Anal.* Calcd for $C_{18}H_{20}N_2O_5S$: C, 57.43; H, 5.36; N, 7.44. Found: C, 57.41; H, 5.34; N, 7.46. IRν_{max}cm^{-1} (Nujol): 1675 (CO). NMR ($CDCl_3$) δ: 1.31 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.02 (3H, s, =C-CH_3), 2.32 (3H, s, Ar-CH_3), 4.25 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.67-7.77 (8H, m, Ar-H), 11.85 (1H, br s, NH). MS *m/z*: 376 (M^+, 32%), 221(BP).

(*E*)-Ethyl Pyruvate 2-[2-(4-Bromobenzenesulfonyloxy)phenylhydrazone] [(*E*)-10b]

Yield: 85%. Pale yellow prisms, mp 116-118 °C (AcOEt-hexane). *Anal.* Calcd for $C_{17}H_{17}BrN_2O_5S$: C, 46.27; H, 3.88; N, 6.35. Found: C, 46.06; H, 3.91; N, 6.33. IRν_{max}cm^{-1} (Nujol): 3100 (NH), 1700 (CO). NMR ($CDCl_3$) δ: 1.36 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.05 (3H, s, =C-CH_3), 4.29 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.70-7.85 (8H, m, Ar-H), 8.04 (1H, br s, NH). MS *m/z*: 442 (M^++2, 8.8%), 440 (M^+, 8.3), 221(BP).

(*Z*)-Ethyl Pyruvate 2-[2-(4-Bromobenzenesulfonyloxy)phenylhydrazone] [(*Z*)-10b]

Yield: 6.5%. Pale yellow prisms, mp 130.5-132 °C (AcOEt-hexane). *Anal.* Calcd for $C_{17}H_{17}BrN_2O_5S$: C, 46.27; H, 3.88; N, 6.35. Found: C, 46.32; H, 3.88; N, 6.36. IRν_{max}cm^{-1} (Nujol): 3250 (NH), 1700 (CO). NMR ($CDCl_3$) δ: 1.36 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.05 (3H, s, =C-CH_3), 4.29 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.70-7.85 (8H, m, Ar-H), 8.04 (1H, br s, NH). MS *m/z*: 442 (M^++2, 8.8%), 440 (M^+, 8.3), 221(BP).

(*E*)-Ethyl Pyruvate 2-[2-(4-Nitrobenzenesulfonyloxy)phenylhydrazone] [(*E*)-10c]

Yield: 38%. Yellow needles, mp 134-135.5 °C (AcOEt-hexane). *Anal.* Calcd for $C_{17}H_{17}N_3O_7S$: C, 50.12; H, 4.21; N, 10.31. Found: C, 50.06; H, 4.15; N, 10.21. IRν_{max}cm^{-1} (Nujol): 3350 (NH), 1685 (CO). NMR ($CDCl_3$) δ: 1.35 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.09 (3H, s, =C-CH_3), 4.28 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.65-8.50 (8H, m, Ar-H), 8.05 (1H, br s, NH). MS *m/z*: 407 (M^+, 22%), 221(BP).

(*Z*)-Ethyl Pyruvate 2-[2-(4-Nitrobenzenesulfonyloxy)phenylhydrazone] [(*Z*)-10c]

Yield: 49%. Yellow needles, mp 137-139 °C (AcOEt-hexane). *Anal.* Calcd for $C_{17}H_{17}N_3O_7S$: C, 50.12; H, 4.21; N, 10.31. Found: C, 50.06; H, 4.15; N, 10.21. IRν_{max}cm^{-1} (Nujol): 3350 (NH), 1685 (CO). NMR ($CDCl_3$) δ: 1.35 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.09 (3H, s, =C-CH_3), 4.28 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.65-8.50 (8H, m, Ar-H), 8.05 (1H, br s, NH). MS *m/z*: 407 (M^+, 22%), 221(BP).

(*E*)-Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)phenylhydrazone] [(*E*)-10d]

Yield: 81%. Colorless needles, mp 101-104 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 48.15; H, 5.39; N, 9.32. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1725 (CO). NMR ($CDCl_3$) δ: 1.34 (3H, t, *J*=6 Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, =C-CH_3), 3.20 (3H, s, SO_2CH_3), 4.28 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.80-7.80 (4H, m, Ar-H), 8.27 (1H, br s, NH). MS *m/z*: 300 (M^+, 50%), 221(BP).

(*Z*)-Ethyl Pyruvate 2-[2-(Methanesulfonyloxy)phenylhydrazone] [(*Z*)-10d]

Yield: 9.8%. Pale yellow needles, mp 108.5-111 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 48.03; H, 5.37; N, 9.28. IRν_{max}cm^{-1} (Nujol): 3240 (NH), 1678 (CO). NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.22 (3H, s, =C-CH_3), 3.30 (3H, s, SO_2CH_3), 4.34 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.70-7.80 (4H, m, Ar-H), 12.25 (1H, br s, NH). MS *m/z*: 300 (M^+, 67%), 221(BP).

(*E*)-Ethyl Pyruvate 2-[2-(Trifluoromethanesulfonyloxy)phenylhydrazone] [(*E*)-10e]

Yield: 83%. Pale orange needles, < mp 30 °C. IRν_{max}cm^{-1} (Nujol): 1710 (CO). NMR ($CDCl_3$) δ: 1.37 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, =C-CH_3), 4.31 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.70-7.50 (3H, m, Ar-

H), 7.72 (1H, dd, *J*= 8, 3 Hz, 3-H), 7.80 (1H, br s, NH). MS *m/z* : 354 (M^+, 33%), 221(52). High Resolution MS *m/z* : Calcd for $C_{12}H_{13}F_3N_2O_5S$: 354.0498. Found: 354.0477.

Fischer Indolization of 2-Sulfonyloxyphenylhydrazones

A) General Procedure for the Fischer Indolization with PPA

A mixture of the hydrazone (**10**) and PPA (10 times the weight of **10**) was heated as described in Table 1. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The crude residue was purified with column chromatography and recrystallized to afforded the indoles (**15** and **16**).

B) General Procedure of the Fischer Indolization with TsOH-Benzene:

To a solution of TsOH (4 eq, freshly prepared from $TsOH•H_2O$ using Dean-Stark apparatus) in benzene was added the hydrazone (**10**) (1 eq) and refluxed for time described in Table 1. Work-up as above afforded the indoles (**15**, **16** and **17**)

1) Normal Product

Ethyl 7-(*p*-Toluenesulfonyloxy)indole-2-carboxylate (15a)

Colorless needles, mp 135-136 °C (benzene-hexane). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.23; H, 4.81; N, 3.89. IRν_{max}cm^{-1}(Nujol): 3260 (NH), 1710 (CO). NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.41 (3H, s, Ar-CH_3), 4.39 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.65-7.85 (8H, m, Ar-H), 9.00 (1H, br s, NH).

Ethyl 7-(4-Bromobenzenesulfonyloxy)indole-2-carboxylate (15b)

Colorless prisms, mp 164-166 °C (benzene-hexane). *Anal.* Calcd for $C_{17}H_{14}BrNO_5S$: C, 48.13; H, 3.33; N, 3.30. Found: C, 48.17; H, 3.40; N, 3.29. IRν_{max}cm^{-1}(Nujol): 3255 (NH), 1710 (CO). NMR ($CDCl_3$) δ: 1.40 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.38 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.60-7.85 (8H, m, Ar-H), 9.00 (1H, br s, NH). MS *m/z* : 425 (M^++2, 12%), 423 (M^+, 11), 204 (BP).

Ethyl 7-(4-Nitrobenzenesulfonyloxy)indole-2-carboxylate (15c)

Orange needles, mp 171-173 °C (EtOH). *Anal.* Calcd for $C_{17}H_{14}N_2O_7S$: C, 52.31; H, 3.61; N, 7.18. Found: C, 52.26; H, 3.59; N, 7.22. IRν_{max}cm^{-1} (Nujol): 3310 (NH), 1680 (CO). NMR ($CDCl_3$) δ: 1.38 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.36 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.45-7.60 (4H, m, Ar-H), 7.94 and 8.24 (each 2H, d, *J*=8 Hz, Ar-H of sulfonyl group), 9.10 (1H, br s, NH). MS *m/z* : 425 (M^++2, 9.1%), 423 (M^+, 8.7), 204 (BP).

Ethyl 7-(Methanesulfonyloxy)indole-2-carboxylate (15d)

Colorless needles, mp 108.5-111 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94. Found: C, 51.04; H, 4.65; N, 4.97. IRν_{max}cm^{-1}(Nujol): 3345 (NH), 1710 (CO). NMR ($CDCl_3$) δ: 1.44 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 3.26 (3H, s, SO_2CH_3), 4.44 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.90-7.71 (4H, m, Ar-H), 9.40 (1H, br s, NH). MS *m/z* : 283 (M^+, 39%), 204 (BP).

Ethyl 7-(Trifluoromethanesulfonyloxy)indole-2-carboxylate (15e)

Colorless needles, mp 85-87 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{10}F_3NO_5S$: C, 42.73; H, 2.99; N, 4.15. Found: C, 42.84; H, 2.97; N, 4.29. IRν_{max}cm^{-1}(Nujol): 3275 (NH), 1705 (CO). NMR ($CDCl_3$) δ: 1.43 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.44 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 7.16 (1H, d, *J*=8 Hz, 4- or 6-H), 7.29 (1H, d, *J*=2 Hz, 3-H), 7.70 (1H, d, *J*=8 Hz, 6- or 4-H), 9.12 (1H, br s, NH). MS *m/z* : 337 (M^+, 24%), 158 (BP).

2) Abnormal Product

Ethyl 5-(*p*-Toluenesulfonyloxy)indole-2-carboxylate (16a = 17)

Colorless prisms, mp 164-166 °C (benzene). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.03; H, 4.74; N, 3.97. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 1.42 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.44 (3H, s, Ar-CH_3), 4.42 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.85-7.80 (8H, m, Ar-H), 9.18 (1H, br s, NH). MS *m/z* : 359 (M^+, 22%), 204 (BP).

Ethyl 5-(4-Bromobenzenesulfonyloxy)indole-2-carboxylate (16b)

Colorless prisms, mp 173.5-174.5 °C (benzene-hexane). *Anal.* Calcd for $C_{17}H_{14}BrNO_5S$: C, 48.13; H, 3.33; N, 3.30. Found: C, 48.36; H, 3.30; N, 3.29. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1700 (CO). NMR ($CDCl_3$) δ: 1.44 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.42 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.75-7.83 (8H, m, Ar-H), 9.20 (1H, br s, NH). MS *m/z* : 390 (M^+, 26%), 204 (BP).

Ethyl 5-(4-Nitrobenzenesulfonyloxy)indole-2-carboxylate (16c)

Pale yellow needles, mp 209-212 °C (EtOH). *Anal.* Calcd for $C_{17}H_{14}N_2O_7S$: C, 52.31; H, 3.61; N, 7.18. Found: C, 52.01; H, 3.60; N, 7.04. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1685 (CO). NMR (400 MHz, DMSO-d_6) δ: 1.33 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.34 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.92 (1H, dd, *J*= 8.8, 2.4 Hz, 6-H), 7.15 (1H, d, *J*=1.5 Hz, 3-H), 7.38 (1H, d, *J*=2.4 Hz, 4-H), 7.41 (1H, d, *J*=8.8 Hz, 7-H), 8.12 and 8.43 (each 2H, d, *J*=9.0 Hz, Ar-H of sulfonyl group), 12.13 (1H, br s, NH). MS *m/z* : 390 (M^+, 17%), 204 (BP).

Ethyl 5-(Methanesulfonyloxy)indole-2-carboxylate (16d)

Pale yellow needles, mp 155-159 °C (EtOH). *Anal.* Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94. Found: C, 51.03; H, 4.72; N, 4.90. IRν_{max}cm^{-1} (Nujol): 3290 (NH), 1680 (CO). NMR (400 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J*=7.1 Hz, $CH_2C\underline{H}_3$), 3.16 (3H, s, SO_2CH_3), 4.43 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2CH_3$), 7.23 (1H, m, 3-H), 7.25 (1H, dd, *J*=8.8, 2.4 Hz, 6-H), 7.44 (1H, d, *J*=8.8 Hz, 7-H), 7.61 (1H, d, *J*=2.4 Hz, 4-H), 9.12 (1H, br s, NH). MS *m/z* : 283 (M^+, 29%), 204 (BP).

Ethyl 5-(Trifluoromethanesulfonyloxy)indole-2-carboxylate (16e)

Colorless needles, mp 133-136 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{10}F_3NO_5S$: C, 42.73; H, 2.99; N, 4.15. Found: C, 42.71; H, 3.00; N, 4.29. IRν_{max}cm^{-1} (Nujol): 3310 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 1.42 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.43 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 7.22 (1H, dd, *J*=9, 2 Hz, 6-H), 7.25 (1H, m, 3-H), 7.46 (1H, d, *J*=9 Hz, 7-H), 7.64 (1H, d, *J*=2 Hz, 4-H), 9.75 (1H, br s, NH). MS *m/z* : 337 (M^+, 24%), 207 (BP).

Alternative Synthesis of Fischer Products

Ethyl 7-(*p*-Toluenesulfonyloxy)indole-2-carboxylate (15a)

Sulfonylation of ethyl 7-hydroxyindole-2-carboxylate[20] (**18**) (1 eq) with *p*-TsCl (1.1 eq) and Et_3N (1.1 eq) in CH_2Cl_2 at 0 °C for 10 min, followed by usual work-up afforded colorless needles (**15a**) (73%), mp 129-129.5 °C (benzene-hexane). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.00; H, 4.70; N, 3.98. IRν_{max}cm^{-1} (Nujol): 3250 (NH), 1700 (CO). NMR ($CDCl_3$) δ: 1.40 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, Ar-CH_3), 4.37 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.61-7.80 (8H, m, Ar-H), 8.90 (1H, br s, NH). MS *m/z* : 359 (M^+, 17%), 204 (BP).

Ethyl 5-(*p*-Toluenesulfonyloxy)indole-2-carboxylate (16a)

Sulfonylation of ethyl 5-hydroxyindole-2-carboxylate[21] (**19**) (1 eq) with *p*-TsCl (4eq) and Et_3N (6 eq) in CH_2Cl_2 at 0 °C for 15 min, followed by usual work-up afforded colorless prisms (**16a**) (98%), mp 162-164

°C (benzene). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.07; H, 4.70; N, 3.91. IRν_{max}cm^{-1} (Nujol): 3320 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 1.40 (3H, t, *J*=7 Hz, $CH_2C\underline{H_3}$), 2.43 (3H, s, Ar-CH_3), 4.42 (2H, q, *J*=7 Hz, $OC\underline{H_2}CH_3$), 6.83-7.80 (8H, m, Ar-H), 9.26 (1H, br s, NH). MS *m/z*: 359 (M^+, 26%), 204 (BP).

Ethyl 5-(Methanesulfonyloxy)indole-2-carboxylate (16d)

Sulfonylation of ethyl 5-hydroxyindole-2-carboxylate[21] (**19**) (1 eq) with MsCl (4 eq) and Et_3N (6 eq) in CH_2Cl_2 at 0 °C for 15 min, followed by usual work-up afforded pale yellow needles (**16d**) (53%), mp 156-158.5 °C (EtOH). *Anal.* Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94. Found: C, 50.91; H, 4.61; N, 4.89. IRν_{max}cm^{-1} (Nujol): 3290 (NH), 1685 (CO). NMR ($CDCl_3$) δ: 1.43 (3H, t, *J*=7 Hz, $CH_2C\underline{H_3}$), 3.14 (3H, s, SO_2CH_3), 4.43 (2H, q, *J*=7 Hz, $OC\underline{H_2}CH_3$), 7.15-7.65 (4H, m, Ar-H), 9.27 (1H, br s, NH). MS *m/z* : 283 (M^+, 37%), 204 (BP).

Ethyl 5-(Trifluoromethanesulfonyloxy)indole-2-carboxylate (16e)

Sulfonylation of ethyl 5-hydroxyindole-2-carboxylate[21] (**19**) (1 eq) with Tf_2O (3 eq) and 2, 6-lutidine (7 eq) in CH_2Cl_2 at 0 °C for 15 min, followed by usual work-up afforded colorless needles (**16e**) (100%), mp 134-136 °C (benzene-hexane). *Anal.* Calcd for $C_{12}H_{10}F_3NO_5S$: C, 42.73; H, 2.99; N, 4.15. Found: C, 42.43; H, 3.00; N, 4.28. IRν_{max}cm^{-1} (Nujol): 3300 (NH), 1695 (CO). NMR ($CDCl_3$) δ: 1.43 (3H, t, *J*=7 Hz, $CH_2C\underline{H_3}$), 4.45 (2H, q, *J*=7 Hz, $OC\underline{H_2}CH_3$), 7.16 (1H, dd, *J*=8, 2 Hz, 6-H), 7.20 (1H, m, 3-H), 7.32 (1H, d, *J*=8 Hz, 7-H), 7.57 (1H, d, *J*=2 Hz, 4-H), 9.40 (1H, br s, NH). MS *m/z* : 337 (M^+, 33%), 204 (BP).

These compounds were identical with the products obtained from the Fischer indolization.

Preparation of 2-Sulfonyloxyphenylhydrazone from Various Ketones

2-Hydrazinophenyl Methanesulfonate *p*-Toluenesulfonate (11) (X = Ms)

Catalytic reduction of 2-nitrophenyl methanesulfonate[22] with Pd-C in EtOH, followed by diazotization and reduction as the method of preparation of 2-hydroxyphenylhydrazine *p*-toluenesulfonate (**13**) gave colorless prisms (**11**) (41%), mp 197-198.5 °C (EtOH). *Anal.* Calcd for $C_7H_{10}N_2O_3S \cdot C_7H_8O_3S$: C, 44.91 H, 4.85; N, 7.48. Found: C, 44.62; H, 4.77; N, 7.41. IRν_{max}cm^{-1} (Nujol): 3260 (NH). NMR (DMSO-d_6) δ: 2.30 (3H, s, Ar-CH_3), 3.42 (3H, s, SO_2CH_3), 6.70-7.60 (8H, m, Ar-H). MS *m/z* : 202 (M^+, 21% as free base), 123 (BP).

1, 2-Cyclohexanedione 2-(2-Methanesulfonyloxy)phenylhydrazone (31)

To a solution of isoamyl nitrite (0.67 mL, 5 mmol) in EtOH (10 mL) was added a mixture of 2-aminophenyl methanesulfonate (0.936 g, 5 mmol) and conc. HCl (2.2 mL, 24 mmol) in EtOH (25 mL) under ice-cooling. To a mixture of 2-hydroxymethylenecyclohexanone[23] (0.76 g, 6 mmol), 50% KOH aq. (1.7 mL), and ice (20 g) in EtOH (15 mL) was added dropwise above diazonium salt solution under ice-cooling, and the whole was stirred at the same temperature for 1.5 h. Usual work-up afforded the title compound (**31**) (32%). Reddish brown plates, mp 115-117 °C (AcOEt-EtOH). *Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C, 52.47; H, 5.50; N, 9.35. IRν_{max}cm^{-1} (Nujol): 1635 (CO). NMR ($CDCl_3$) δ: 1.60-2.00 (4H, m, aliphatic-H_2), 2.20-3.00 (4H, m, aliphatic-H_2), 3.33 (3H, s, SO_2CH_3), 6.90 and 7.23 (each 1H, dt, *J*=8, 2 Hz, 4- and 5-H), 7.30 (1H, dd, *J*=8, 2 Hz, 6-H), 7.73 (1H, dd, *J*=8, 2 Hz, 3-H), 13.75 (1H, br s, NH). MS *m/z* : 296 (M^+, 72%), 108 (BP).

3-(2, 3-Piperidinedione) (2-Methanesulfonyloxy)phenylhydrazone (33)

To a solution of 2-aminophenyl methanesulfonate (1.906 g, 10 mmol) in EtOH was added conc. HCl (4.4 mL, 50 mmol) and isoamyl nitrite (1.4 mL, 10 mmol) under ice-cooling. To a mixture of 3-ethoxycarbonylpiperidinone[24] (2.454 g, 14 mmol), 50% KOH aq. (3.4 mL), and ice (40 g) in EtOH (30 mL) was added dropwise above diazonium salt solution under ice-cooling. Usual work-up afforded the title compound (**33**) (37%) as yellow needles, mp 168.5-171 °C (AcOEt-EtOH). *Anal.* Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.08; N, 14.13. Found: C, 48.36 H, 5.10; N, 13.95. IRν_{max}cm^{-1} (Nujol): 3310 and 3170 (NH), 1660 (CO). NMR ($CDCl_3$) δ: 1.78-2.17 (2H, m, 5'-H_2), 2.70 (2H, t, *J*=6 Hz, 4'-H_2), 3.07-3.55 (2H, m, 6'-H_2), 3.17 (3H, s, SO_2CH_3), 6.60-7.65 (5H, m, Ar-H and NH), 13.30 (1H, br s, NH). MS *m/z*: 297 (M^+, 46%), 218 (BP).

Fischer Indolization of Hydrazones from Various Ketones

1) From Isolated 2-Sulfonyloxyphenyhydrazones (31 and 33)

The reaction was carried out with TsOH in benzene as described in the Fischer indolization of hydrazones of ethyl pyruvate (**10**).

2) Without Isolation of 2-Sulfonyloxyphenylhydrazone (25)

a) From 2-Mesyloxyphenylhydrazine•TsOH (11): 8-(Methanesulfonyloxy)-1, 2, 3, 4-tetrahydrocarbazole (27b) To a suspension of the 2-mesyloxyphenyhydrazine•TsOH (**11**) (0.392 g, 1.05 mmol) in CH_2Cl_2 (1.5 mL) was added cyclohexanone (0.119 mL 1.15 mmol) and Et_3N until the precipitates were disappeared under ice-cooling. After work-up the crude hydrazone (**25a**) (194 mg) was treated with TsOH (0.415 g, 2.2 mmol) in benzene (10 mL) under Fischer indolization condition. Usual work-up afforded colorless prisms (0.099 g, 36% from **11**), mp 114-116 °C (benzene-hexane). *Anal.* Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.54; H, 5.71; N, 5.35. NMR ($CDCl_3$) δ: 1.50-2.20 (4H, m, 2- and 3-H_2), 2.30-2.90 (4H, m, 1- and 4-H_2), 3.12 (3H, s, SO_2CH_3), 6.80-7.50 (3H, m, Ar-H), 8.32 (1H, br s, NH). MS *m/z*: 265 (M^+, 32%), 186 (100).

b) From 2-Hydroxyphenyhydrazine (13): 8-(*p*-Toluenesulfonyloxy)-1, 2, 3, 4-tetrahydrocarbazole (27a): Typical Procedure

To a suspension of 2-hydroxyphenylhydrazine•TsOH (**13**) (1.043 g, 3.5 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.665 mL, 5.3 mmol) and cyclohexanone (0.399 mL, 3.9 mmol) under Ar atmosphere, and the whole was stirred at 0 °C for 30 min. To this mixture was added Et_3N (0.665 mL, 5.3 mmol) and a solution of *p*-TsCl (0.665 g, 3.5 mmol) in CH_2Cl_2 (5 mL), and the whole was stirred at 0 °C for 30 min. After work-up the crude hydrazone (**25a**) (1.433 g) was treated with TsOH (1.332 g, 7 mmol) in benzene (57 mL) under Fischer indolization condition. Usual work-up afforded colorless prisms (**27a**) (0.869 g, 72% from **13**), mp 134-135 °C (benzene-hexane). *Anal.* Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.85; H, 5.59; N, 4.07. IRν_{max}cm^{-1} (Nujol): 3420 (NH). NMR ($CDCl_3$) δ: 1.60-2.05 (4H, m, 2- and 3-H_2), 2.36 (3H, s, Ar-CH_3), 2.50-2.90 (4H, m, 1- and 4-H_2), 6.37 (1H, d, *J*=8 Hz, 7-H), 6.74 (1H, t, *J*=8 Hz, 6-H), 7.05-7.42 (3H, m, Ar-H), 7.65 (2H, d, *J*=8 Hz, 2'- and 6'-H), 8.14 (1H, br s, NH). MS *m/z*: 341 (M^+, 46%), 186 (BP).

7-(*p*-Toluenesulfonyloxy)cyclopent[*b*]indole (28)

Colorless needles, mp 170-173 °C (AcOEt-hexane). *Anal.* Calcd for $C_{18}H_{17}NO_3S$: C, 66.04; H, 5.23; N, 4.28. Found: C, 65.96; H, 5.23; N, 4.34. IRν_{max}cm^{-1} (Nujol): 3350 (NH). NMR ($CDCl_3$) δ: 2.40 (3H, s, Ar-CH_3), 2.51-3.13 (6H, m, 1-, 2- and 3-H_2), 6.38 (1H, d, *J*=8 Hz, 4-H), 6.77 (1H, t, *J*=8 Hz, 5-H), 7.21

(3H, d, *J*=8 Hz, Ar-H), 7.67 (2H, d, *J*=8 Hz, 2'- and 6'-H), 8.33 (1H, br s, NH). MS *m/z*: 327 (M^+, 44%), 172 (BP).

4-(*p*-Toluenesulfonyloxy)cyclohept[*b*]indole (29)

Colorless prisms, mp 158-160 °C (AcOEt-hexane). *Anal.* Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67.63; H, 5.94; N, 3.79. IRν_{max}cm^{-1} (Nujol): 3408 (NH). NMR (400 MHz, $CDCl_3$) δ: 1.73-1.82 (4H, m, aliphatic-H_2), 1.84-1.92 (2H, m, aliphatic-H_2), 2.44 (3H, s, Ar-CH_3), 2.77 (2H, dif t, *J*=5.5 Hz, 6- or 10-H_2), 2.81 (2H, dif d, *J*=5.5 Hz, 10- or 6-H_2), 6.39 (1H, d, *J*=7.8 Hz, 1- or 3-H), 6.82 (1H, t, *J*=7.8 Hz, 2-H), 7.29 (2H, d, *J*=8.3 Hz, 3'- and 5'-H), 7.30 (1H, d, *J*=7.8 Hz, 3- or 1-H), 7.73 (2H, d, *J*=8.3 Hz, 2'- and 6'-H), 8.11 (1H, br s, NH). MS *m/z*: 355 (M^+, BP).

2-(*p*-Toluenesulfonyloxy)cyclohept[*b*]indole (30)

Colorless needles, mp 129.5-132.5 °C (benzene-hexane). *Anal.* Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67.83; H, 5.96; N, 3.65. IRν_{max}cm^{-1} (Nujol): 3392 (NH). NMR (400 MHz, $CDCl_3$) δ: 1.70-1.81 (4H, m, aliphatic-H_2), 1.85-1.91 (2H, m, aliphatic-H_2), 2.43 (3H, s, Ar-CH_3), 2.67 (2H, dif t, *J*=5.9 Hz, 6- or 10-H_2), 2.80 (2H, dif d, *J*=5.9 Hz, 10- or 6-H_2), 6.61 (1H, dd, *J*=8.8, 2.4 Hz, 3-H), 7.06 (1H, d *J*=8.8 Hz, 4-H), 7.08 (1H, d, *J*=2.4 Hz, 1-H), 7.28 (2H, d, *J*=8.3 Hz, 3'- and 5'-H), 7.71 (2H, d, *J*=8.3 Hz, 2'- and 6'-H), 7.70 (1H, br s, NH). MS *m/z*: 355 (M^+, 15%), 200 (BP).

8-(Methanesulfonyloxy)-1-oxo-1, 2, 3, 4-tetrahydrocarbazole (32)

Colorless needles, mp 202-204°C (AcOEt-EtOH). *Anal.* Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 55.84; H, 4.72; N, 4.92. IRν_{max}cm^{-1} (Nujol): 3260 (NH), 1660 (CO). NMR ($CDCl_3$) δ: 2.25-2.35 (2H, quintet, *J*=6.2 Hz, 3-H_2), 2.72 (2H, t, *J*=6.2 Hz, 4-H_2), 3.02 (2H, t, *J*=6.2 Hz, 2-H_2), 3.26 (3H, s, SO_2CH_3), 7.15 (1H, t, *J*=8,Hz, 6-H), 7.34 and 7.62 (each 1H, d, *J*=8 Hz, 7- and 5-H), 9.69 (1H, br s, NH). MS *m/z*: 279 (M^+, 95%), 200 (BP).

8-(Methanesulfonyloxy)-1-oxo-1, 2, 3, 4-tetrahydropyrido[3, 4-*b*]indole (34)

Colorless prisms, mp 200-203 °C (AcOEt). *Anal.* Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.31; N, 9.99. Found: C, 51.37 H, 4.30; N, 9.87. IRν_{max}cm^{-1} (Nujol): 3340 and 3120 (NH), 1650 (CO). NMR (400 MHz, DMSO-d_6) δ: 2.95 (2H, t, *J*=7.0 Hz, 4-H_2), 3.49 (3H, s, SO_2CH_3), 3.52 (2H, dt, *J*=6.8, 2.4 Hz, 3-H_2), 7.11 (1H, t, *J*=7.3 Hz, 6-H), 7.21 (1H, dd, *J*=7.3, 0.7 Hz, 5- or 7-H), 7.61 (1H, d, *J*=7.3 Hz, 7- or 5-H), 7.69 (1H, t like, NH), 12.12 (1H, br s, NH). MS *m/z*: 280 (M^+, 61%), 201 (BP).

6-(Methanesulfonyloxy)-1-oxo-1, 2, 3, 4-tetrahydropyrido[3, 4-*b*]indole (35)

Colorless prisms, mp 216-219 °C (AcOEt). *Anal.* Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.31; N, 9.99. Found: C, 51.39 H, 4.39; N, 9.78. IRν_{max}cm^{-1} (Nujol): 3360 and 3180 (NH), 1650 (CO). NMR (400 MHz, DMSO-d_6) δ: 2.93 (2H, t, *J*=7.0 Hz, 4-H_2), 3.35 (3H, s, SO_2CH_3), 3.51 (2H, dt, *J*=7.0, 2.4 Hz, 3-H_2), 7.19 (1H, dd, *J*=8.8, 2.2 Hz, 7-H), 7.45 (1H, d, *J*=8.8 Hz, 8-H), 7.60 (1H, d, *J*=2.2 Hz, 5-H), 7.67 (1H, t like, NH), 11.86 (1H, br s, NH). MS *m/z*: 280 (M^+, 39%), 201 (BP).

2-Ethyl-3-methyl-7-(*p*-toluenesulfonyloxy)indole (36)

Colorless prisms, mp 108-112.5 °C ($CHCl_3$-hexane). *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.50; H, 5.82; N, 4.17. IRν_{max}cm^{-1} (KBr): 3400 (NH). NMR (400 MHz, $CDCl_3$) δ: 1.25 (3H, t, *J*=7.5 Hz, 2-$CH_2\underline{CH_3}$), 2.20 (3H, s, 3-CH_3), 2.43 (3H, s, Ar-CH_3), 2.72 (2H, q, *J*=7.5 Hz, 2-$\underline{CH_2}CH_3$), 6.46 (1H, d, *J*=7.8 Hz, 6-H), 6.84 (1H, t, *J*=7.8 Hz, 5-H), 7.31 (1H, d, *J*=7.8 Hz, 4-H), 7.28 and 7.72 (each 2H, d, *J*=8.3 Hz, Ts-aromatic H), 8.09 (1H, br s, NH). MS *m/z*: 329 (M^+, 24%), 174 (BP).

2-Ethyl-3-methyl-5-(*p*-toluenesulfonyloxy)indole (37)

Colorless needles, mp 121-122.5 °C (benzene-hexane). *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.87; H, 5.71; N, 4.05. IRν_{max}cm^{-1}(KBr): 3410 (NH). NMR (400 MHz, $CDCl_3$) δ: 1.26 (3H, t, *J*=7.5 Hz, 2-$CH_2\underline{CH_3}$), 2.12 (3H, s, 3-CH_3), 2.44 (3H, s, Ar-CH_3), 2.73 (2H, q, *J*=7.5 Hz, 2-$\underline{CH_2}CH_3$), 6.65 (1H, dd, *J*=8.5, 2.5 Hz, 6-H), 7.08 (1H, d, *J*=2.5 Hz, 4-H), 7.09 (1H, d, *J*=8.5 Hz, 7-H), 7.28 and 7.71 (each 2H, d, *J*=8.3 Hz, Ts-aromatic H), 7.74 (1H, br s, NH). MS *m/z*: 329 (M^+, 13%), 174 (BP).

Total Synthesis of Eudistomidin-A (2)

(*E*)-Ethyl Pyruvate 2-[(4-Bromo-2-hydroxyphenyl)hydrazone] (43)

To a solution of 2-amino-5-bromophenol[18] (**42**) (5.342 g, 28 mmol) and conc. HCl (11 mL, 114 mmol) in a mixture of acetonitrile (30 mL) and water (30 mL), was added a solution of $NaNO_2$ (2.07 g, 30 mmol) in water (30 mL) at 0°C. The resulting diazonium salt solution was added to a solution of ethyl α-methylacetoacetate (3.94 mL, 28 mmol) in EtOH (30 mL), keeping alkaline by adding 50% KOH aq. at 0°C. After the addition was over, the reaction mixture was poured into ice-water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give solid (7.22 g). The crude product was column-chromatographed over silica gel using hexane-AcOEt to give the title compound (**43**) (5.132 g, 60%). Recrystallization from AcOEt-hexane gave pale orange needles, mp 177-179 °C. *Anal.* Calcd for $C_{11}H_{13}BrN_2O_3$: C, 43.87; H, 4.35; N, 9.30. Found: C, 43.91; H, 4.40; N, 9.32. IR ν_{max}cm^{-1} (Nujol): 3290 (NH), 1683 (C=O). NMR (DMSO-d_6) δ: 1.26 (3H, t, *J*=7 Hz, $CH_2\underline{CH_3}$), 2.05 (3H, s, C-CH_3), 4.20 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 6.87 (1H, dd, *J*=9, 2 Hz, 5-H), 6.95 (1H, d, *J*=2 Hz, 3-H), 7.18 (1H, d, *J*=9 Hz, 6-H), 8.90 and 10.50 (each 1H, s, NH and OH, disappeared by addition of D_2O). MS *m/z*: 302 (M^++2, 55%), 300 (M^+, 56%), 186 (BP).

(*E*)- and (*Z*)-Ethyl Pyruvate 2-[4-Bromo-2-(*p*-toluene-sulfonyloxy)phenylhydrazone] (44)

To a solution of ethyl pyruvate 2-(4-bromo-2-hydroxyphenyl)hydrazone (**43**) (9.101 g, 30 mmol) in pyridine (80 mL) was added TsCl (9.795 g, 51 mmol) under ice-cooling and the whole was stirred at room temperature for 4 h. The reaction mixture was then concentrated *in vacuo* to about half volume, poured into 10% HCl containing ice, and extracted with AcOEt. The organic layer washed with 10% HCl, sat. $NaHCO_3$aq, and brine, and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave a red oil (15.41 g), which was column-chromatographed over silica gel using hexane-AcOEt to give (*E*)- (7.133 g, 52%) and (*Z*)- (2.953 g, 22%) of the title compound (**44**).

(*E*)-44: Pale pink needles, mp 110-111.5 °C (AcOEt-hexane). *Anal.* Calcd for $C_{18}H_{19}BrN_2O_5S$; C, 47.48; H, 4.21; N, 6.15. Found: C, 47.46; H, 4.23; N, 6.23. IR ν_{max}cm^{-1} (Nujol): 3300 (NH), 1680 (CO). NMR δ: 1.34 (3H, t, *J*=7 Hz, $CH_2\underline{CH_3}$), 2.00 (3H, s, C-CH_3), 2.43 (3H, s, Ar-CH_3), 4.28 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 6.92-7.90 (7H, m, Ar-H), 8.00 (1H, br s, NH). MS *m/z*: 456 (M^++2, 36%), 454 (M^+, 33%), 299 (BP).

(*Z*)-44: Pale orange prisms, mp 116-117 °C (AcOEt-hexane). *Anal.* Calcd for $C_{18}H_{19}BrN_2O_5$: C, 47.48; H, 4.21; N, 6.15. Found: C, 47.36; H, 4.19; N, 6.18. IR ν_{max}cm^{-1} (Nujol): 3200 (NH), 1680 (C=O). NMR δ: 1.36 (3H, t, *J*=7 Hz, $CH_2\underline{CH_3}$), 2.08 (3H, s, C-CH_3), 2.40 (3H, s, Ar-CH_3), 4.30 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 7.10-7.50 (5H, m, Ar-H), 7.76 (2H, d, *J*=8 Hz, 2' and 6'-H), 11.90 (1H, br s, NH). MS *m/z*: 456 (M^++2, 49%), 454 (M^+, 45%), 299 (BP).

Ethyl 5-Bromo-7-(*p*-toluenesulfonyloxy)indole-2-carboxylate (45)

(*E*)-Ethyl pyruvate 2-[4-bromo-2-(*p*-toluenesulfonyloxy)phenylhydrazone] (**44**) (3.279 g, 7.2 mmol) was mixed with polyphosphoric acid (PPA) (33 g) and CH_2Cl_2 (2 mL), and the mixture was heated with stirring at 80 °C for 1 h. The reaction mixture was, while still hot, poured into hot water and stirred until black tar disappeared. After cooling it was extracted with AcOEt, washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a black tarry oil (1.878 g). The column chromatography over silica gel using hexane-AcOEt gave the title compound (**45**) (1.278 g, 41%). Recrystallization gave colorless needles, mp 126-127 °C. *Anal.* Calcd for $C_{18}H_{16}BrNO_5$: C, 49.33; H, 3.68; N, 3.20. Found: C, 49.21; H, 3.68; N, 3.23. IR ν_{max} cm^{-1} (Nujol): 3240 (NH), 1700 (C=O). NMR (400Mz) δ: 1.42 (3H, t, *J*=7 Hz, $CH_2\underline{CH_3}$), 2.45 (3H, s, Ar-CH_3), 4.41 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 6.92 (1H, d, *J*=1.5 Hz, 4 or 6-H), 7.12 (1H, d, *J*=2 Hz, 3-H), 7.34 (1H, d, *J*=8.5 Hz, 3' and 5'-H), 7.69 (1H, m, 4 or 6-H), 7.76 (2H, d, *J*=8.5 Hz, 2' and 6'-H), 9.06 (1H, br s, NH). MS *m/z*: 439 (M^++2, 47%), 437 (M^+, 44%), 282 (BP).

The same reaction with TsOH in benzene gave the indole (**45**) in 55% yield.

5-Bromo-7-(*p*-toluenesulfonyloxy)indole (46)

A mixture of ethyl 5-bromo-7-(*p*-toluenesulfonyloxy)indole-2-carboxylate (**45**) (517 mg, 1.18 mmol) and conc. H_2SO_4 (3 mL) in 50% AcOH aq. (50 mL) was heated at 130°C for 10 h in a sealed tube. The reaction mixture was poured into water (50 mL) and the resulting precipitates (477 mg, 99%), mp 270-276 °C, were collected with suction. This compound was 5-bromo-7-(*p*-toluenesulfonyloxy)indole-2-carboxylic acid as shown bellow. NMR (DMSO-d_6) δ: 2.24 (3H, s, Ar-CH_3), 6.97 (1H, d, *J*=1.5 Hz, 4 or 6-H), 7.09 (1H, d, *J*=2.0 Hz, 3-H), 7.43 (2H, d, *J*=8 Hz, 3' and 5'-H), 7.83 (1H, d, *J*=1.7 Hz, 4 or 6-H), 7.87 (2H, d, *J*=8 Hz, 2' and 6'-H), 12.37 (1H, br s, NH), 13.26 (1H, br s, OH). MS *m/z*: 411 (M^++2, 53%), 409 (M^+, 51%), 91 (BP). This compound was used for next reaction without further purification and characterization.

A mixture of 5-bromo-7-(*p*-toluenesulfonyloxy)indole-2-carboxylic acid (908 mg, 2.21 mmol) and copper-chromite[25] (133 mg) in quinoline (35 mL) was heated with stirring under Ar atmosphere at 200 °C for 2.5 h. The reaction mixture was poured into 10% HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a brown oil (795 mg), which was column-chromatographed over silica gel using hexane-AcOEt to give the title compound (**46**) (603 mg, 74%). Recrystallization from AcOEt-hexane gave colorless prisms, mp 120.5-121 °C. *Anal.* Calcd for $C_{15}H_{12}BrNO_3S$: C, 49.19; H, 3.30; N, 3.82. Found: C, 49.13; H, 3.26; N, 3.86. IR ν_{max} cm^{-1} (Nujol): 3380 (NH). NMR (400 MHz) δ: 2.46 (3H, s, Ar-CH_3), 6.50 (1H, dd, *J*=2 and 3 Hz, 2 or 3-H), 6.68 (1H, d, *J*=2 Hz, 4 or 6-H), 7.23 (1H, t, *J*=3 Hz, 2 or 3-H), 7.33 (2H, d, *J*=8 Hz, 3' and 5'-H), 7.63 (1H, m, 4 or 6-H), 7.74 (2H, d, *J*=8 Hz, 2' and 6'-H), 8.74 (1H, br s, NH). MS *m/z*: 367 (M^++2, 46%), 365 (M^+, 44%), 210 (BP).

5-Bromo-7-(*p*-toluenesulfonyloxy)indole-3-carboxaldehyde (47)

A solution of 5-bromo-7-tosyloxyindole (**46**) (603 mg, 1.65 mmol) in *N,N*-dimethylformamide (DMF) (2 mL) was added to a solution of $POCl_3$ (0.384 mL, 4.12 mmol) in DMF (1 mL) at 0° C under Ar atmosphere and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into water, basified with sat. $NaHCO_3$ and warmed at 80 °C for 30 min. After cooling at room temperature, the mixture was extracted with AcOEt, washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. Evaporation of the solvent gave pale brown crystals (621 mg, 96%), which were recrystallized from AcOEt-EtOH-hexane to give colorless needles, mp 210.5-212 °C. *Anal.* Calcd for $C_{16}H_{12}BrNO_4S$: C, 48.75; H, 3.07; N, 3.55. Found: C, 48.69; H, 3.08; N, 3.58. IR ν_{max} cm^{-1} (Nujol): 3150 (NH), 1640 (C=O).

NMR (DMSO-d_6) δ: 2.38 (3H, s, Ar-CH_3), 6.92 (1H, d, *J*=2 Hz, 4 or 6-H), 7.38 (2H, d, *J*=8 Hz, $C_{3'}$ and $C_{5'}$-H), 7.78 (2H, d, *J*=8 Hz, C2' and C6'-H), 8.08(1H, d, *J*= 2 Hz, 4 or 6-H), 8.27 (1H, d, *J*=3 Hz, 2-H), 9.85 (1H, s, CHO), 12.60 (1H, br s, NH). MS *m/z*: 395 (M^++2, 47%), 393 (M^+, 46%), 91 (BP).

(*E*)-5-Bromo-3-nitrovinyl-7-(*p*-toluenesulfonyloxy)indole (48)

Nitromethane (3 mL) was added to a mixture of 5-bromo-7-(*p*-toluenesulfonyloxy)indole-3-carboxaldehyde (**47**) (150 mg, 0.38 mmol) and $AcONH_4$ (73 mg, 0.95 mmol) under Ar atmosphere and the mixture was refluxed for 3 h. After almost nitromethane was evaporated, the residue was poured into water and extracted with AcOEt. Organic layer was washed with brine and dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave yellowish brown crystals (166 mg, 100%), mp 205-209 °C. *Anal.* Cacld for $C_{17}H_{13}BrN_2O_5S$: C, 46.70; H, 3.00; N, 6.41. Found: C, 46.72; H, 3.01; N, 6.37. IR ν_{max} cm^{-1} (Nujol): 3370 (NH). NMR (400 MHz) (DMSO-d_6) δ: 2.40 (3H, s, Ar-CH_3), 6.97 (1H, d, *J*=1.5 Hz, 4 or 6-H), 7.46 (2H, d, *J*=8 Hz, 3' and 5'-H), 7.83 (2H, d, *J*=8 Hz, 2'and 6'-H), 8.14 (1H, d, *J*=13.5 Hz, vinyl-H), 8.23 (1H, d, *J*=1.5 Hz, 4 or 6-H), 8.27 (1H, br d, 2-H), 8.35 (1H, d, *J*=13.5 Hz, vinyl-H), 12.68 (1H, br s, NH). MS *m/z*: 438 (M^++2, 40%), 436 (M^+, 36%), 91 (BP).

5-Bromo-7-(*p*-toluenesulfonyloxy)-N_b-[*N*-(*t*-butoxycarbonyl)prolyl]tryptamine (49)

A solution of (*E*)-5-bromo-3-nitrovinyl-7-(*p*-toluenesulfonyloxy)indole (**48**) (44 mg, 0.10 mmol) in THF (1 mL) was added to a suspension of $LiAlH_4$ (38 mg, 1 mmol) in THF (1 mL) at 0°C under Ar atmosphere and the whole was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water containing 5% NaOH aq. (1 mL) and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give 5-bromo-7-(*p*-toluenesulfonyloxy)-tryptamine (31 mg, 72%) as a brown oil. MS *m/z*: 410 (M^++2, 9%), 408 (M^+, 9%), 155 (BP). This compound was used for the next reaction without further purification.

To a solution of 5-bromo-7-(*p*-toluenesulfonyloxy)tryptamine (31 mg, 0.084 mmol) and Boc-proline (18.2 mg, 0.084 mmol) in DMF (1 mL) was added Et_3N (0.012 mL, 0.084 mmol) and diethyl phosphorocyanidate (DEPC) (0.013 mL, 0.084 mmol) under ice-cooling and Ar atmosphere, and the whole was stirred at room temperature for 30 min. The reaction mixture was poured into 3% $NaHCO_3$ aq. and extracted with AcOEt, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a pale brown oil (41 mg, 89%), which was column-chromatographed over silica gel using AcOEt-hexane to give the title compound (**49**) as pale brown amorphous (29 mg, 63%). IR ν_{max} cm^{-1} (Nujol): 3250 (NH), 1660 (C=O). NMR (400 MHz) δ: 1.41 (9H, m, *t*-Bu), 1.61-2.43 (4H, m, 3' and 4'-H), 2.46 (3H, s, Ar-CH_3), 2.77-3.00 (2H, m, ind-CH_2-), 3.15-3.63 (4H, m, ind-CH_2CH_2-N), 4.24 (1H, br. s, 2'-H), 6.67 (1H, d, *J*=1.5 Hz, 4 or 6-H), 7.10 (1H, m, 2-H), 7.34 (2H, d, *J*=8.5 Hz, 3" and 5"-H), 7.59 (1H, *J*=1.5 Hz, 4 or 6-H), 7.75 (2H, d, *J*=8.5 Hz, 2" and 6"-H), 8.75 (1H, br s, ind-NH). FABMS *m/z*: 608 (M^++H+2, 5%), 606 (M^++H, 5%), 70 (BP). HR FABMS Calcd. for $C_{27}H_{32}BrN_3O_6S$: 605.1187. Found: 605.1185.

6-Bromo-3,4-dihydro-1-(2-pyrrolinyl)-8-(*p*-toluenesulfonyloxy)-β-carboline (50)

A solution of 5-bromo-7-(*p*-toluenesulfonyloxy)-N_b-[*N*-(*t*-butoxycarbony)prolyl]tryptamine (**49**) (72 mg, 0.118 mmol) in dichloroethane (4.4 mL) was added to PPE (5.4 g) under Ar atmosphere and the whole was refluxed for 1.2 h. After evaporated the solvent, water (5.4 g) was added to this residue. The whole was stirred at room temperature for 4 h, adjusted to pH 9.5 with 20% KOH aq. and extracted with benzene. The organic layer was washed with brine dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give brown oil (95 mg). This oil was column-chromatographed over silica gel using AcOEt-hexane to give pale yellow

needles (10 mg, 18%), mp 158-162 °C. IR ν_{max} cm^{-1} (Nujol): 3340 (NH). NMR (400 MHz) δ: 1.99 (2H, quintet, *J*=7.5 Hz, 4'-H), 2.43 (3H, s, Ar-CH_3), 2.86 (2H, t, *J*=8.5 Hz, 4-H), 2.95 (2H, br t, *J*=8 Hz, 3'-H), 4.10 (2H, t, *J*=8.5 Hz, 3-H), 4.20 (2H, br.t, *J*=7 Hz, 5'-H), 6.86 (1H, d, *J*=1.5 Hz, 5 or 7-H), 7.31 (2H, d, *J*=1.8 Hz, 3" and 5"-H), 7.58 (2H, d, *J*=1 Hz, 5 or 7-H), 7.76 (1H, d, *J*=8 Hz, 2" and 6"-H), 10.61 (1H, br s, NH). MS *m/z*: 487 (M^++2, 39%), 485 (M^+, 41%), 330 (BP). HR MS Calcd. for $C_{22}H_{20}BrN_3O_3S$: 485.0404. Found: 485.0377.

***O*-(*p*-Toluenesulfonyl)eudistomidin-A (51)**

A solution of 6-bromo-3,4-dihydro-1-(2-pyrrolinyl)-8-(*p*-toluenesul-fonyloxy)-β-carboline (**50**) (34 mg, 0.070 mmol) in absolute $CHCl_3$ (8 mL) was added to active MnO_2 (342 mg) under ice-cooling and Ar atmosphere, and whole was stirred under reflux for 1 h. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to give a pale brown oil (30 mg). Column-chromatography over silica gel using AcOEt-hexane gave the title compound (**51**) (21 mg, 61%). Recrystallization from AcOEt-hexane gave pale brown needles, mp 189-190 °C. NMR (400 MHz) δ: 2.10 (2H, quintet, *J*=8 Hz, 4'-H), 3.27 (2H, br t, *J*=8 Hz, 3'-H), 4.29 (2H, br t, *J*=7.5 Hz, 5'-H), 7.26-7.30 (3H, m, 3", 5" and 5 or 7-H), 7.78 (2H, d, *J*=8 Hz, 2" and 6"-H), 7.90 (1H, d, *J*=5.5 Hz, 4-H), 8.14 (1H, d, *J*=1.5 Hz, 5 or 7-H), 8.52 (1H, d, *J*=5.5 Hz, 3-H), 10.90 (1H, br s, NH). MS *m/z*: 485 (M^++2, 16%), 483 (M^+, 15%), 328 (BP). HR MS Calcd. for $C_{22}H_{18}BrN_3O_3S$: 483.0248. Found: 483.0224.

Eudistomidin-A (2)

O-(*p*-Toluenesulfonyl)eudistomidin-A (**51**) (7.0 mg, 0.014 mmol) was added to a solution of KOH (6.5 mg, 0.099 mmol) in EtOH (1 mL) and the whole was stirred at room temperature for 1.3 h. The reaction mixture was poured into water, acidified to pH 5 with 10% HCl aq., and then basified to pH 10 with 10% NH_4OH aq. The mixture was extracted with AcOEt, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave the target compound (**2**) as pale yellow solid (5.2 mg, 72%), mp 265-280 °C.[14, 19] NMR (400 MHz, DMSO-d_6) δ: 2.02 (2H, m, 4'-H), 3.21 (2H, m, 3'-H), 3.35 (1H, br. s, OH), 4.25 (2H, m, 5'-H), 7.10 (1H, d, *J*=2 Hz, 7-H), 8.02 (1H, d, *J*=2 Hz, 5-H), 8.25 (1H, d, *J*=5 Hz, 4-H), 8.46 (1H, d, *J*=5 Hz, 3-H), 11.2 (1H, br s, NH). MS *m/z*: 331 (M^++2, 99%), 329 (M^+, BP). HR MS Calcd. for $C_{15}H_{12}BrN_3O$: 329.0161. Found: 329.0119.

The synthetic eudistomidin-A (**2**) was identified with the natural one.

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