Anomalous Substituent Effects in the Bischler−Napieralski Reaction of 2-Aryl Aromatic Formamides

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Treatment of some 1-naphthylformamides (or formanilides) possessing a 2,4,5-trioxygenated phenyl substituent at the 2-position with $POCl_3$ caused an unprecedented carbon insertion reaction into a benzene ring, producing 7-5 ring (azaazulene) systems as valence isomers of isoquinoline skeletons. Precise examination of this abnormal Bischler−Napieralski reaction (BNR) using various substrates led to the following scope and limitations: (i) the 7-5 ring systems were constructed when either 2-alkoxy-4,5-methylenedioxyphenyl- or 4,5-dialkoxy-2-hydroxyphenyl-substituted formamides were used as a starting substrate; (ii) in the former case the formyl carbon was inserted into the C_1-C_6 bond of the 2-phenyl group, and normal isoquinoline cyclization competed with an abnormal carbon insertion reaction; (iii) the presence of a hydroxy group at the 2′-position as in the latter cases caused exclusive carbon insertion, in which alternative C_1-C_2 insertion products were quantitatively formed; (iv) 3,6-dimethoxy-2-hydroxyphenyl-substituted formanilide electronically equivalent to 4,5-dialkoxy-2-hydroxy derivatives produced an indole−pyrone as an abnormal BNR product. Theoretical approaches using the PM-3 method indicated that these abnormal BNRs could be triggered by ipso attack at the 1′-position yielding spiro intermediates. Ring cleavege of the six-membered ring in the spiro intermediates to a ketene function followed by recyclization was proposed for the 2′-hydroxy-directed abnormal BNRs leading to the C_1-C_2 insertion product or the indole−pyrone derivative.

Introduction

Traditional Bischler−Napieralski reaction (BNR) is one of the most important synthetic tools for the construction of isoquinoline skeleton.[1] Although many kinds of dehydrating agents such as phosphoric acid and sulfonic acid derivatives are available for BNR, we have applied BNR using phosphorus oxychloride ($POCl_3$) as a dehydrating agent to the construction of isoquinoline skeletons from 2-aryl-*N*-methyl-1-naphthylformamides in the final step of the synthesis of benzo[*c*]phenanthridine alkaloids for the structure−activity relationship of their antitumor activity.[2] In general, direction of the cyclization in the BNRs of 2-aryl-1-naphthylformamides is strictly controlled by the substitution pattern of alkoxy functions on the 2-aryl substituent. Thus, in the case of 2-(3,4-dialkoxyphenyl)-1-naphthylformamides[3] **1** exclusive cyclization to the *para* position to the 3′-alkoxy group has occurred to quantitatively yield 8,9-dialkoxy O_4-bases[4] **2** (*para*-orientation),[5] but not isomeric 7,8-dialkoxy O_4-ones[4] **3**. On the other hand, application of BNR to 2-(4,5-dialkoxy-2-methoxyphenyl)-1-naphthylformamides[6] **4** has afforded 7,8-dialkoxy-10-methoxy O_5-bases[4] **5** as *ortho*-orientation products because an electronically more activated 2′-position to be cyclized is blocked by the presence of an additional methoxy group (Scheme 1).

In the synthetic studies of macarpine[7] (**7**), an O_6-base,[4] we found that an unexpected 12-azonianaphth[1.2-*b*]-azulene (a 7-5 ring system in the rings A and B)[8] **8**, which was produced by the insertion of a formamide carbon into the C_1-C_6 bond of the 2-aryl group in the naphthylformamide **6**, was concomitantly produced together with an expected isoquinoline product (a 6−6 ring system) **7**,

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(1) (a) Whaley, W. M.; Govindachari, T. R. *Organic Reactions*; Adams, R., Ed.; John-Wiley and Sons: New York, 1951; Vol 6, pp 74−150. (b) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279−1300. (c) Fowler, F. W. *Comprehensive Hetrocyclic Chemistry*; Katrirzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol 2, pp 410−416.

(2) Ishii, H.; Ichikawa, Y.-I.; Kawanabe, E.; Ishikawa, M.; Ishikawa, T.; Kuretani, K.; Inomata, M.; Hoshi, A. *Chem. Pharm. Bull.* **1985**, *33*, 4139−4151.

(3) (a) Ishii, H.; Chen, I.-S.; Ueki, S.; Akaike, M.; Ishikawa, T. *Chem. Pharm. Bull.* **1987**, *35*, 2717−2725. (b) Ishii, H.; Chen, I.-S.; Ishikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 671−676. (c) Green, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1647−1648.

(4) See: Ishikawa, T. *Hetrocycles* **1999**, *50*, 627−639 and references therein.

(5) Calculation of electron density of the 2-aryl group in 2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (**1**: $2R_1 = CH_2$; $R_2 = Me$) using the AM-1 method with CAChe ver. 3.6 showed higher electron density at C6′ (4.0981) than at C2′ (4.0888), supporting the *para*-orientation in BNR.

(6) Ishii, H.; Ishikawa, T.; Ichikawa, Y.-I.; Sakamoto, M. *Chem. Pharm. Bull.* **1977**, *25*, 3120−3121. (b) Ishii, H.; Watanabe, T.; Ishikawa, T. *Chem. Pharm. Bull.* **1978**, *26*, 3252−3254. (c) Ishii, H.; Ishikawa, T.; Watanabe, T.; Ichikawa, Y.-I.; Kawanabe, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2283−2289.

(7) Ishikawa, T.; Saito, T.; Ishii, H. *Tetrahedron* **1995**, *51*, 8447−8458.

(8) Ishikawa, T.; Saito, T.; Noguchi, S.; Ishii, H.; Ito, S.; Hata, T. *Tetrahedron Lett.* **1995**, *36*, 2795−2798.

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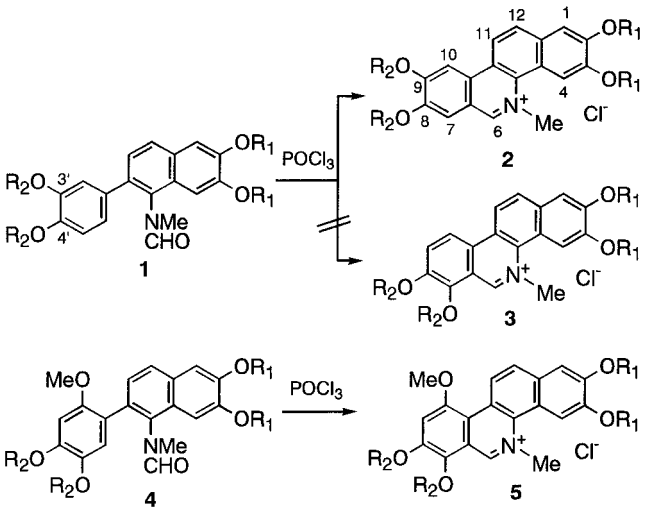
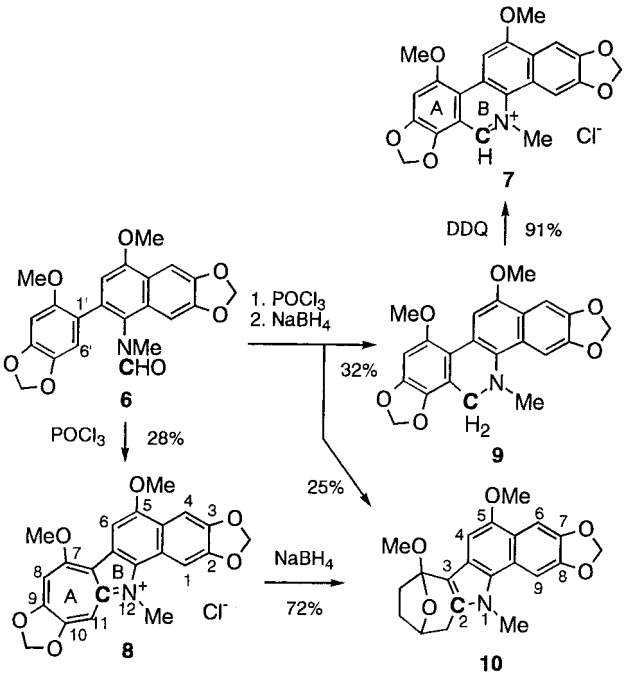
Scheme 1



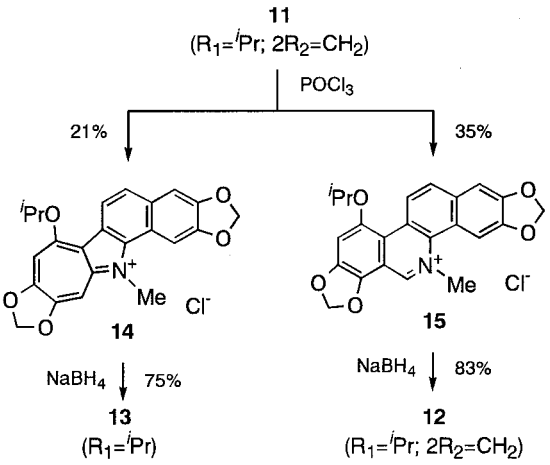
Scheme 2



and that sodium borohydride ($NaBH_4$) reduction of the azoniaazulene **8** led to the formation of benz[*g*]indole **10** fused to a 1-alkoxy-8-oxabicylo[3.2.1]octa-2-ene skeleton[8] (see Scheme 2).

Extensive examination of this new carbon insertion reaction (abnormal BNR) using related aromatic formamides such as 2,4,5-trioxygenated phenyl-substituted naphthylformamides **11** and phenolic 2-arylformanilides **20** led to the following conclusions: (i) 2-alkoxy-4,5-methylenedioxy or 4,5-dialkoxy-2-hydroxy functions on the 2-aryl-substituted formamides play crucial roles for the construction of 7-5 ring systems (azaazulenes) as valence isomers of isoquinoline skeletons; (ii) in the latter cases the 7-5 ring systems are given as sole abnormal BNR products; (iii) carbon insertion occurs beween the C_1-C_6 bond of the 2-aryl group when 2-alkoxy-4,5-methylenedioxyphenyl-substituted formamides are subjected to BNR; (iv) an alternative carbon insertion into the C_1-C_2 bond of the 2-aryl group is observed in the case of 4,5-dialkoxy-2-hydroxyphenyl-substituted formamides; (v) thus, direction of the insertion is strictly dependent upon the nature of oxygen functions in the 2-aryl substituent; (vi) on the other hand, 3,6-dimethoxy-2-hydroxyphenyl-substituted formanilide, electronically equivalent to 4,5-dialkoxy-2-hydroxy derivatives, produced an indole−pyrone as an abnormal BNR product. In this paper we present not only the scope and limitation of these anomalous carbon insertions into a benzene ring producing 7-5 ring systems, but also the formation of an indole product under the conditions of BNR.

Scheme 3



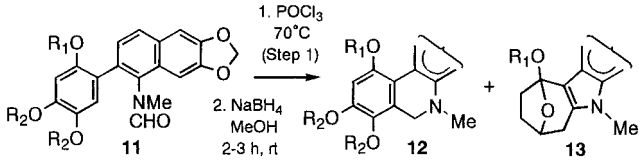
Results and Discussion

(1) BNRs of 2-Aryl-1-naphthylformamides. Preliminary BNR of 4-methoxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-1-(*N*-methylformamido)naphthalene (**6**) for macarpine (**7**) synthesis gave a red brown solid **8** different from an expected **7** in ca. 40% yield. The same molecular formula of the product as that of **7** was suggested by its fast atom bombardment mass spectrum (FABMAS); however, its ^1H NMR spectrum showed that it was a mixture contaminated with small amounts of **7**. Therefore, we tried to isolate the BNR product(s) after reduction. Treatment of **6** with $POCl_3$ followed by $NaBH_4$ reduction afforded a benzindole **10** (25%) together with dihydromacarpine (**9**) (32%) which was smoothly converted into macarpine[7] (**7**) by dehydrogenation with DDQ.[6] Opimization of the isolation of BNR product(s) by fractional recrystallization (MeOH−EtOH) successfully afforded a pure azoniaazulene product **8** in 28% yield. Reduction of **8** with $NaBH_4$ gave the benzindole **10** in 72% yield (Scheme 2).

The full structures of an azoniaazulene **8** and a benzindole **10** were determined to be 5,7-dimethoxy-12-methyl-2,3;9,10-bismethylenedioxy-12-azonianaphth[1,2-*b*]azulene chloride and 5-methoxy-2,3-(1-methoxy-8-oxabicylo[3.2.1]octeno)-1-methyl-7,8-methylenedioxybenz[*g*]indole, respectively, based on structural elucidation of the corresponding isopropoxy derivatives as mentioned below (see Scheme 3). This abnormal BNR, producing a 7-5 ring system **8**, made us precisely reexamine BNRs of 1-naphthylformamides **11** with a 2,4,5-trialkoxyphenyl function at the 2-position like **4**, in which normal benzo[*c*]phenanthridine alkaloids had been obtained as isolable products.[6]

On 2-(2,4,5-Trialkoxyphenyl)-1-naphthylformamides 11. 2-(4,5-Dialkoxy-2-isopropoxyphenyl)-1-naphthylformamides **11** ($R_1 = {}^i$Pr; R_2 = Me or $R_2 = -CH_2-$),

Table 1. Reinvestigation of BNRs of 2-(2,4,5-Trialkoxyphenyl)-1-naphthylformamides 11 Followed by $NaBH_4$ Reduction



run	R_1	R_2	R_2	time (h) in step 1	yield (%)[a] 12	13
1	Me	Me	Me	1.5	89[b]	−
2	^{i}Pr	Me	Me	3	91	−
3	Me	CH_2		8	30[c]	30 (R_1 = H)[d]
4	^{i}Pr	CH_2		9	44	22 (R_1 = ^{i}Pr)[d]

[a] Isolated, nonoptimized yields. [b] Isolated as the quaternary chloride before the reduction. The starting formamide is known. The chloride (chelilutine chloride) had been obtained in 56% yield in the previous experiment.[6c] [c] The starting formamide is known. The corresponding quaternary (chelirubine) chloride had been obtained in 30% yield in the previous experiment.[6c] [d] Acetal function (OR_1) was dependent upon the conditions used for workup.

among four naphthylformamides examined, were newly prepared according to our reported method[3] (See Supporting Information).

Treatment of **11** with $POCl_3$ at 70 °C followed by $NaBH_4$ reduction gave cyclized product(s) **12** and/or **13** (Table 1). Exclusive normal cyclization to isoquinoline skeletons **12** was observed when dimethoxy-substituted naphthylformamides **11** (R_2 = Me) were used as substrates (runs 1 and 2), while displacement of the methoxy groups into a methylenedioxy function in **11** led to the production of indole systems **13** in moderate yields along with normal cyclized products **12** (runs 3 and 4). The structures of indole skeletons were established based on the X-ray crystallographic analysis[8] of a benzindole **13** (R_1 = ^{i}Pr) obtained in run 4 in Table 1.

Carefully fractional recrystallization of the crude BNR product of the 2′-isopropoxy-4′,5′-methylenedioxy formamide **11** (R_1 = ^{i}Pr; R_2 = $-CH_2-$) from MeOH led to successful isolation of two products, an azoniaazulene chloride **14** (21%) and an isoquinolinium chloride **15** (35%) as less soluble and more soluble components, respectively. Independent $NaBH_4$ reduction of each quaternary base afforded the same cyclized products obtained in the above two-step reaction of BNR and reduction (Scheme 3). The structure of 7-isopropoxy-12-azoniaazulene skeleton for **14** was determined by precise inspection of its spectral data, especially the NMR data including NOE experiments (see Figure 1), as described in a preliminary communication.[8]

Thus, it was clear that the presence of methylenedioxy function at the 4′ and 5′ positions in 2,4,5-trialkoxyphenyl-substituted naphthylformamides was responsible for the 7-5 ring construction through carbon insertion into the C_1-C_6 bond of the 2-aryl group.

2-(4,5-Dimethoxy-2-hydroxyphenyl)-1-naphthylformamide 16. Next we examined the BNR of 2-(4,5-dimethoxy-2-hydroxyphenyl)-1-naphthylformamide **16** involving a phenolic function at the 2′-position, which had been isolated as isoarnottianamide[9] from plant sources. The phenolic formamide **16** was prepared from an isopropoxyformamide **11** (R_1 = ^{i}Pr; R_2 = Me) by treatment with 10% methanesulfonic acid in chloroform (see Supporting Information). Heating **16** in acetonitrile with $POCl_3$ at 80 °C afforded a single product **17** quantitatively, which was inert to $NaBH_4$ reduction. Its molecular formula was determined to be $C_{21}H_{17}NO_5$ by elemental analysis and high resolution (HR) FABMS. Although no absorption appeared in the typical carbonyl region of the IR spectrum, appearance of a signal at δ 175.2 in the ^{13}C NMR spectrum indicated the presence of a conjugated carbonyl carbon in the molecule. Further inspection of the spectral data (see Experimental Section) allowed us to deduce the product to be an azaazulenone with a 7-5 ring system, which was temporarily supposed to be a C_1-C_6 insertion product **17A** based on the structure of the azoniaazulene **14** produced in the BNR of 2′-isopropoxy-4′,5′-methylenedioxy naphthylformamide **11** (R_1 = ^{i}Pr; R_2 = $-CH_2-$) (Scheme 4).

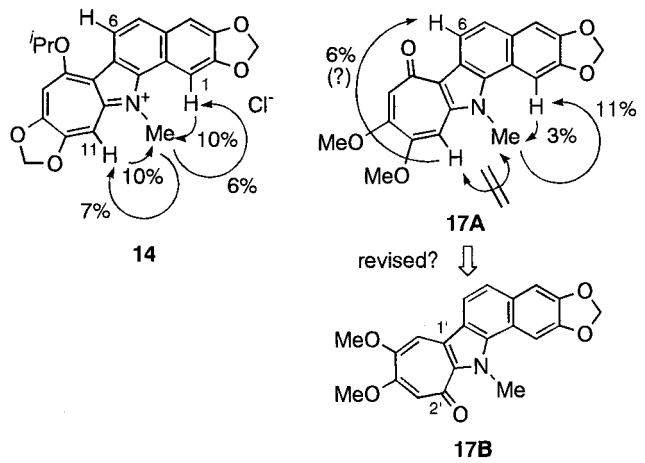
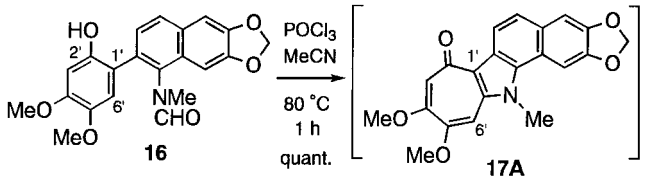


Figure 1. Selected NOE enhancements of 7-5 ring system products **14** and **17**.

Scheme 4

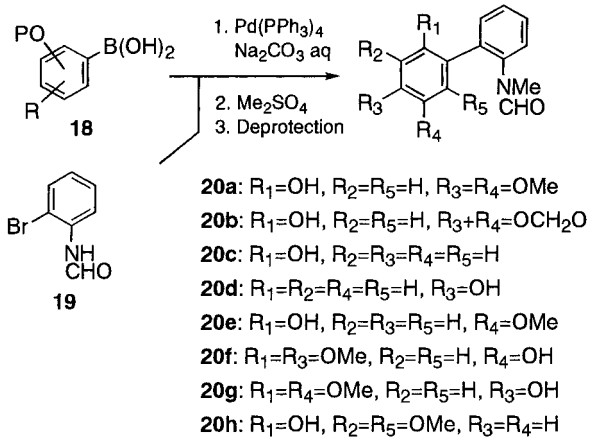


However, NOE experiments of the product indicated some discrepancies for the supposed structure **17A**. The C_1-C_6 insertion product **14** showed NOE enhancements between an *N*-methyl group (δ 4.34) and both singlets due to 1-H (δ 7.93) and 11-H (δ 8.24), respectively, whereas only single NOE enhancement between an *N*-methyl group (δ 4.63) and a singlet (δ 8.12) assignable to 1-H was observed in **17** (Figure 1). Furthermore, no enhancement was detectable between a doublet due to 6-H and any singlet signals in **14**; however, 6% enhancement of the corresponding doublet (δ 8.17) was observed on irradiation of the singlet at δ 7.55 due to a seven-membered ring proton of **17**. These facts suggested that the 7-5 ring system produced in the BNR of a phenolic formamide **16** could be an alternative C_1-C_2 insertion product **17B**.

Unfortunately, in this stage no further information on the correct structure of **17** could be obtained because of their low solubility to usual organic solvents. Trials for preparation of a single crystal for X-ray crystallographic

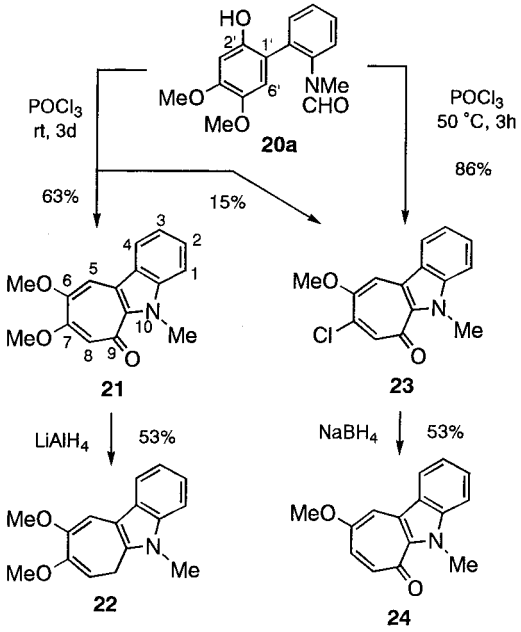
(9) Ishii, H.; Ishikawa, T.; Lu, S.-T.; Chen, I.-S. *Tetrahedron Lett.* **1976**, 1203−1206.

Scheme 5



P=Protecting Group (^{i}Pr or PhCH$_2$)

Scheme 6



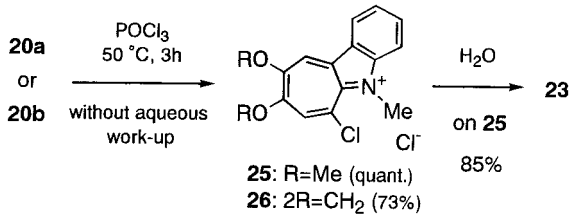
analysis also failed. Therefore, we decided to examine BNRs of phenolic 2-arylformanilides **20** for the scope and limitations of this abnormal cyclization to 7-5 ring systems in addition to structural determination of the azaazulenone product **17**.

(2) BNRs of Phenolic 2-Arylformanilides 20. Phenolic 2-arylformanilides **20** were basically prepared by a Suzuki-type coupling reaction[10] between protected arylboronic acids **18** and 2-bromoformanilide (**19**) followed by methylation and deprotection (Scheme 5). Thus, eight formanilides **20a**−**h** were prepared (see Supporting Information).

2-(4,5-Dialkoxy-2-hydroxyphenyl)formanilides 20a and 20b. At first we examined the BNR of 2-(4,5-dimethoxy-2-hydroxyphenyl)formanilide **20a** having the same substitution pattern as that in the phenolic naphthylformamide **16**. Treatment of **20a** with $POCl_3$ at room temperature afforded a cyclized product **21** in 63% yield (Scheme 6). The expected production of a 7-5 ring system was reasonably deduced by inspection of its spectral data (see Experimental Section).

(10) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178−184.

Scheme 7



Treatment of **21** with lithium aluminum hydride gave a tetrahydro derivative **22** in 53% yield. Reduction of a ketonic function to a methylene unit was indicated by the appearance of an A_2X signal pattern [δ 3.14 (2H, d, J = 7.6 Hz) and δ 4.89 (1H, t, J = 7.6 Hz)] in the ^{1}H NMR spectrum of **22**. Successful preparation of a single crystal for X-ray crystallographic analysis[11] resulted in unambiguously establishing the structure of **22** to be 9*H*-6,7-dimethoxy-10-methylbenz[*b*]azaazulene (see Supporting Information). This indicated that **21** was 9-azaazulenone corresponding to a C_1-C_2 insertion product and that a cyclized product derived from **16** must be C_1-C_2 insertion product **17B**. Thus, NOE enhancements observed in **17** could be reasonably explained by the presence of a carbonyl group at the *peri* position to an indole nitrogen in C_1-C_2 insertion products.

An alternative cyclized product **23** was additionally obtained as a minor product (15% yield) in the above BNR of **20a**. The same **23** was produced in 86% yield when BNR was carried out under heating at 50 °C. Its spectral data showed that **23** was a chlorine-substituted azaazulenone, in which the 7-methoxy group of **21** was displaced by a chlorine atom.[12] Easy dechlorination of **23** to **24** with $NaBH_4$ could support the 7-chloro structure of **23** corresponding to a vinylogous acid chloride moiety (see Scheme 6).

Interestingly, it was found that a relatively labile chlorine-incorporating quaternary azoniaazulene product **25** was quantitatively obtained in the BNR of **20a** without aqueous workup and that aqueous treatment of **25** afforded the chloroazaazulenone **23** in 85% yield.[13] Inspection of the spectral data showed that **25** was 9-chloro-6,7-dimethoxy-10-methyl-10-azoniabenz[*b*]azulene chloride (see Experimental Section). The same type of 9-chloroazoniaazulene **26** was also obtained in the BNR (without aqueous workup)[14] of 2-hydroxyphenyl formanilide **20b** carrying a methylenedioxy function in place of dimethoxy groups in **20a** (Scheme 7). These experimental facts indicated that the location of a hydroxy function at the 2′-position in a 2′,4′,5′-trialkoxy system was inevitable for the cyclization to 7-5 ring systems producing C_1-C_2 insertion products.

Other Phenolic Formanilides 20c−**g**. Next, the other five phenolic formanilides of 2-hydroxyphenyl- **20c**,

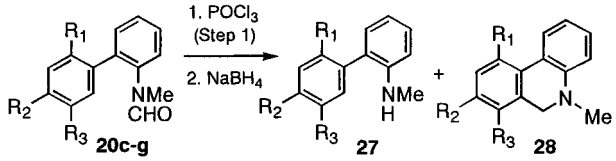
(11) Crystal data for **22**: $C_{16}H_{17}NO_2$ = 255.32, monoclinic, space group $P2_1$ (#4); a = 8.130(9), b = 7.780(9) Å, c = 10.94(2), β = 99.97 (8)°; V = 681(1) Å^3; Z = 2; D_{calc} = 1.244 g/cm^3; μ(Mo Kα) = 1.24 cm^{-1}. A total of 1231 reflections (1229 unique) were recorded on a Rigaku RAXIS-II diffractometer. Anisotropic full-matrix least squares based on F^2 for non-H atoms and isotropic for H atoms converged to a standard agreement factor, R = 0.060, R_w = 0.069, using 1192 reflections [$I > 2\sigma(I)$].

(12) Irradiation of 5-H (δ 7.59) led to 14% and 12% NOE enhancements of 4-H (δ 8.02) and a methoxy signal (δ 4.07), respectively.

(13) Chemical reactivity of azaazulene systems obtained in abnormal BNRs will be discussed elsewhere.

(14) Aqueous workup of **26** afforded a 9-azaazulenone similar to **21** as a sole isolable product; however, the yield was low (11%).

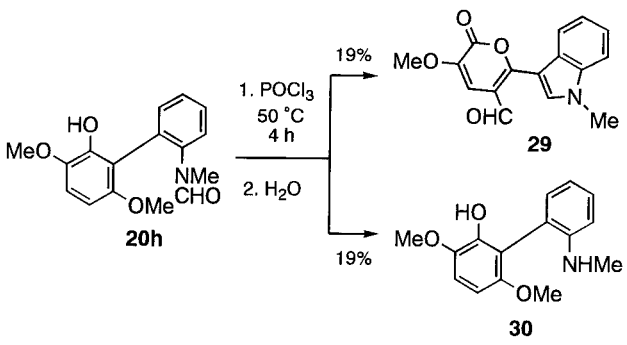
Table 2. BNRs of Other Phenolic 2-Phenylformanilides 20c−g



	R_1	R_2	R_3	Temp (°C) in Step 1	Time (h)	Product(s) (%) 27	28
20c	OH	H	H	70	17	70[a]	—
20d	H	OH	H	50	3	50[b]	—
				120	18	53[c]	—
20e	OH	H	OMe	50	24	76	—
20f	OMe	OMe	OH	50	1.5	—	66[d]
20g	OMe	OH	OMe	50	3	74[d]	—
				120	22	—	41

[a] The starting **20c** was recovered in 11%. [b] The starting **20d** was recovered in 37%. [c] The starting **20d** was recovered in 20%. [d] Isolated before reduction.

Scheme 8

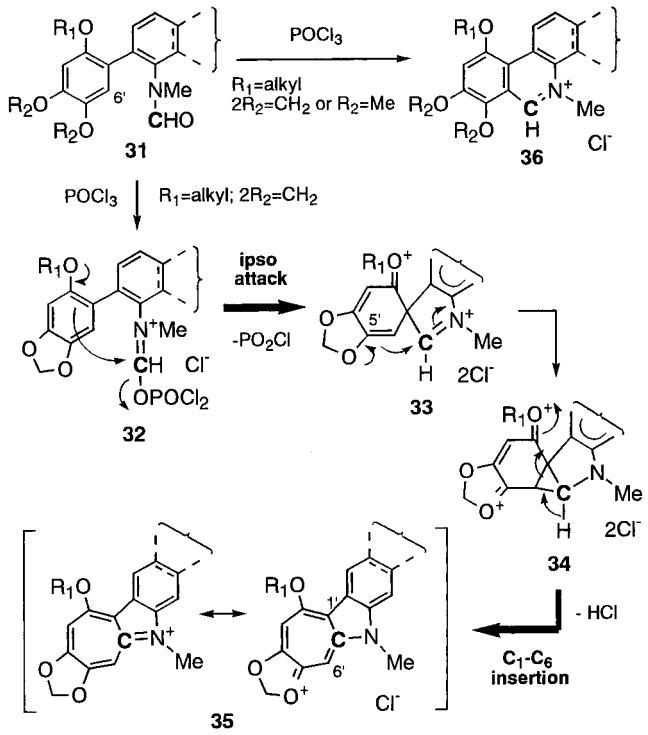


4-hydroxyphenyl- **20d**, 2-hydroxy-5-methoxyphenyl- **20e**, 2,4-dimethoxy-5-hydroxyphenyl- **20f**, and 2,5-dimethoxy-4-hydroxyphenylformanilides **20g** were treated with $POCl_3$ under the conditions given in Table 2, respectively. However, only either deformylation or normal isoquinoline cyclization was observed in all cases, resulting in no production of azaazulene systems.

2-(3,6-Dimethoxy-2-hydroxyphenyl)formanilide 20h. 2-(3,6-Dimethoxy-2-hydroxyphenyl)formanilide[15] **20h** could be supposed to be a synthon of the 4,5-dimethoxy-2-hydroxy system **20a** in the viewpoint of electronic contribution of alkoxy groups to the benzene ring. We finally examined the BNR of **20h**, in which carbon insertion could be the sole expected reaction because of the presence of substituents at both positions to be cyclized. Treatment of **20h** with $POCl_3$ at 50 °C afforded a new indole product **29** with a pyrone ring in 19% yield together with a deformylated product **30** (19%) and a starting **20h** (29%) (Scheme 8).

The molecular formula of **29** was determined to be $C_{16}H_{13}NO_4$ by its HRFABMS. Conjugated lactone and aldehyde functions in its molecule were observed in the IR and ^{13}C NMR spectra. Appearance of a 3H singlet at δ 3.05 and a 1H singlet at δ 7.55 in the ^1H NMR spectrum indicated the presence of 3-substituted *N*-methylindole

Scheme 9



skeleton. Further inspection of the spectral data (see Experimental Section) allowed us to deduce the new product to be an indole−pyrone derivative depicted as **29**, and the structure was completely confirmed by X-ray crystallographic analysis[16] (see Supporting Information). Thus, it was clear that 2′,3′,6′-oxygenated system containing a hydroxy group at the 2′-position caused abnormal BNR giving an indole product accompanied by destruction of a benzene ring.

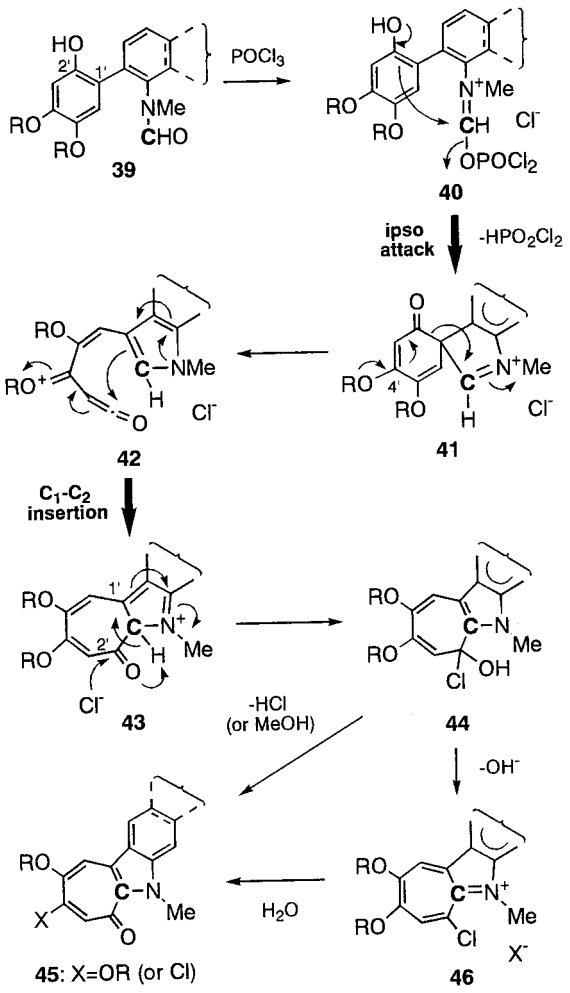
(3) Mechanistic Consideration for Abnormal BNRs. Anomalous carbon insertion reactions into benzene ring during the BNRs of 2-aryl aromatic formamides are summerized as follows: (i) abnormal BNRs are observed in the BNRs of 2′,4′,5′-trioxygenated aromatic formamides; (ii) in the cases of trialkoxy substituents, a methylenedioxy group at the 4′,5′ positions causes the carbon insertion, in which C_1-C_6 insertion is observed, and normal isoquinoline cyclization competes with abnormal insertion reaction; (iii) in the cases of monohydroxy and dialkoxy substituents, the presence of a hydroxy group at the 2′-position is responsible for the exclusive carbon insertion reaction, in which alternative C_1-C_2 insertion products are produced; (iv) on the other hand, 3,6-dimethoxy-2-hydroxyphenyl-substituted formanilide affords an indole−pyrone as an abnormal BNR product.

On the basis of these facts, we supposed a mechanism for abnormal BNRs as shown in Schemes 9−11. In all cases, ipso attack[17] of the formyl carbon[18] to the 1′-

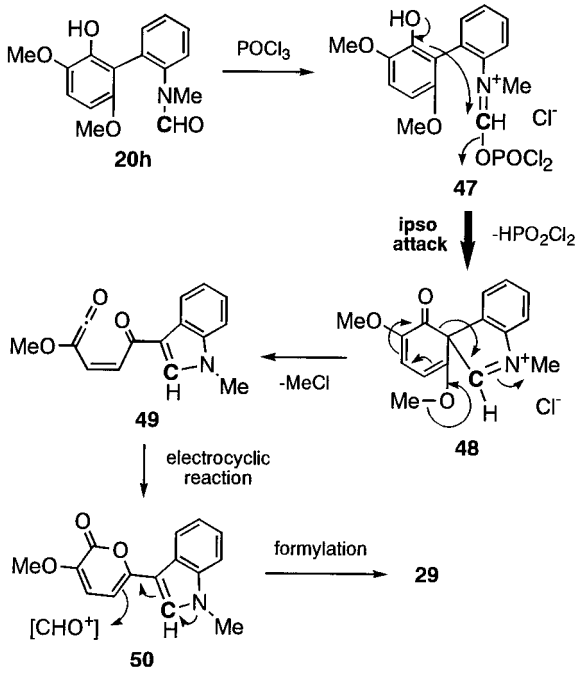
(15) **20h** was prepared from 2-(2,6-dimethoxyphenyl)formanilide obtained by Suzuki-type coupling reaction of **19** and 2,6-dimethoxyphenylboronic acid through seven steps (see Supporting Information).

(16) Crystal data for **29**: $C_{16}H_{13}NO_4 = 283.28$, orthorhombic, space group $P2_12_12_1$ (#19); $a = 7.987(10)$, $b = 22.97(2)$, $c = 7.255(5)$ Å; $V = 1330(2)$ Å^3; $Z = 4$; $D_{calc} = 1.414$ g/cm^3; μ(Mo Kα) = 1.03 cm^{-1}. 1213 independent reflections were recorded on a Rigaku RAXIS-II diffractometer. Anisotropic full-matrix least squares based on F^2 for non-H atoms and isotropic for H atoms converged to a standard agreement factor, $R = 0.069$, $R_w = 0.083$, using 1047 reflections [$I > 3\sigma(I)$].

Scheme 10



Scheme 11



position doubly activated by 2′,4′- or 2′,6′-dioxygen functions should initiate the reaction to give spiro intermediates[17b,19] such as **33** in Scheme 9.

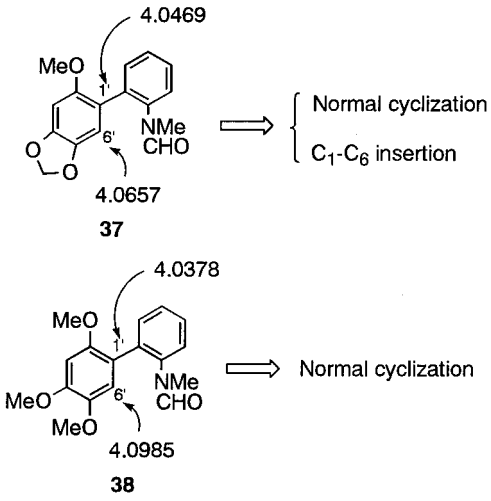


Figure 2. Selected calculated electron density of 2-(2,4,5-trialkoxyphenyl)formanilides **37** and **38**.

2-Alkoxy-4,5-methylenedioxyphenyl Formamides: C_1-C_6 Insertion Reaction. In 2-alkoxy-4,5-methylenedioxyphenyl formamides **31** ($R_2 = -CH_2-$) a fused 6-3-6 ring system **34** could be formed by the C−C bond formation at the 2-position of the indolenium skeleton of a spiro compound **33** triggered by the 5′-oxygen group after ipso attack in an activated amide **32**.[20] Valence isomerization of **34** into a 7-5 ring system **35** results in carbon insertion into the C_1-C_6 bond of the 2-aryl group (Scheme 9).

In contrast, only normal isoquinoline cyclization was observed in the BNRs of formamides **31** (R_2 = Me) with 4,5-dimethoxyphenyl function. These facts could be explained by more effective conjugation of a methoxy group to a benzene ring rather than a methylenedioxy group.[21] Thus, in the 4,5-dimethoxyphenyl-substituted formamides the 6′-position would be reactive enough to be directly attacked by the formyl carbon, exclusively yielding an isoquinoline skeleton **36** (R_2 = Me).

To rationalize the reactivities of the BNR mentioned above, MO calculations on the 2-aryl substituent in 2-(2,4,5-trialkoxyphenyl)formanilides **37** and **38** by the PM-3 method[22] were performed (Figure 2). In these systems a main reaction course is a normal isoquinoline cyclization due to direct attack of the formyl carbon at the more electron-rich 6′-position. However, the 1′- and 6′-positions in **37** carrying a methylenedioxy function show closer electron density ($\Delta_{6'-1'} = 0.0188$) than in **38**

(17) (a) March, J. *Advanced Organic Chemistry*, 3rd. ed.; Wiley-Interscience: New York; 1985; pp 458−459. (b) For BNR, see Doi, S.; Shirai, N.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2217−2221.

(18) In the preliminary communication[8] carbene insertion into the benzene ring had been supposed for the ring expansion. However, a substituent-dependent direction in carbon insertions required the proposed mechanism to be revised.

(19) Kusama, H.; Yamashita, Y.; Uchiyama, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 965−975.

(20) A similar dichlorophosphorate had been supposed as a reactive intermediate in the BNR of 4-methoxyphenylethylbenzamide, in which migration of a carbon unit through a spiro compound producing an isomeric isoquinoline was observed together with an expected isoquinoline formation.[17b]

(21) (a) Buckley, T. F., III; Rapport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056−3062. (b) Sha, C.-K.; Young, J.-J.; Yeh, C.-P.; Cheng, S.-C.; Wang, S.-L. *J. Org. Chem.* **1991**, *56*, 2694−2696. (c) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115−119.

(22) MO calculations were performed by the PM-3 method with MOPAC ver 6.0. Results were obtained after full optimization of possible geometries.

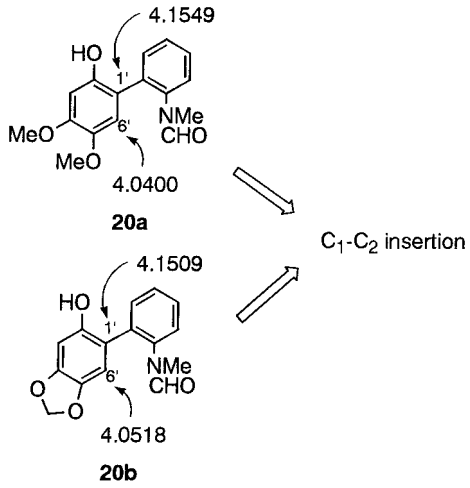


Figure 3. Selected calculated electron density of 2-(4,5-dialkoxy-2-hydroxyphenyl)formanilides **20a** and **20b**.

carrying a dimethoxy function ($\Delta_{6'-1'} = 0.0607$). Thus, ipso attack to the 1′-position, resulting in the formation of a C_1-C_6 carbon insertion product, could be expected to compete with normal isoquinoline cyclization in the former case as shown in the BNRs of the related naphthylformamides such as **6** and **11** ($R_2 = -CH_2-$).

4,5-Dialkoxy-2-hydroxyphenyl Formamides: C_1-C_2 Insertion Reaction. An alternative reaction route must be active for exclusive C_1-C_2 carbon insertion observed in the 2-hydroxyphenyl formamide **39**. A spiro ketone **41** should be produced by ipso attack because of the presence of a hydroxy group at 2′-position. Participation of 4′-alkoxy group could cause ring cleavage to give a ketene indole **42**. Nucleophilic attack of the enamine function of an indole skeleton to the ketene unit results in carbon insertion into the C_1-C_2 bond of 2-aryl group affording a 7-5 ring system **43**.[23] Final products **45** or **46** are dependent upon workup conditions[24] used (Scheme 10).

This speculation is also supported by similar MO calculations of 2-(4,5-dialkoxy-2-hydroxyphenyl)formanilides **20a** and **20b** by the PM-3 method[22] (Figure 3). Preferential ipso attack at more electron-rich 1′-position ($\Delta_{1'-6'} = 0.1149$ in **20a**; $\Delta_{1'-6'} = 0.0991$ in **20b**) should be responsible for the exclusive formation of C_1-C_2 insertion products.

3,6-Dimethoxy-2-hydroxyphenyl Formamide: Destruction of the Benzene Ring. It could be also supposed that a spiro ketone **48** and a ketene indole **49** are formed as reactive intermediates in the BNR of 2-(3,6-dimethoxy-2-hydroxyphenyl)formanilide **20h**. The substitution pattern of alkoxy groups in the hexadienone ring of **48** leads to a conjugate ketene **49** without a cationic charge by ring cleavage triggered by the 6′-methoxy group. A 6π system of the ketene unit in **49** causes to electrocyclic reaction to give a lactone **50**,[23] and the subsequent Vilsmeyer−Haack type formylation with an activated amide such as **47** produces indole−pyrone **29** (Scheme 11).

(23) The outline of this mechanism was suggested by one of the reviewers. We thank him for this valuable suggestion of a more reasonable mechanism than our original one.

(24) In the BNR of **20a** use of P_2O_5 in hot toluene instead of $POCl_3$ afforded 6,7-dimethoxyazaazulenone **21** in 46% yield as a sole product.

Conclusions

In conclusion, it was found that fused azaazulene ring systems triggered by carbon insertion into a benzene ring were constructed when 2-alkoxy-4,5-methylenedioxyphenyl or 4,5-dialkoxy-2-hydroxyphenyl systems among aromatic formamides[25] with a 2,4,5-trialkoxyphenyl substituent at the 2-position were subjected to BNR and that direction of carbon insertion could be controlled by their substituent patterns. Furthermore, C_1-C_2 insertion was suggested to be a normal reaction path in the latter BNR. In fact we have observed that some modified formanilides with a 4,5-dimethoxy-2-hydroxyphenyl system afford 9-azaazulenones as sole cyclized products in expected high yields.[26] In addition, an indole−pyrone derivative, the pyrone unit of which would be derived from a benzene ring, was obtained as an alternative BNR product in the case of a 3,6-dialkoxy-2-hydroxy system. Thus, these abnormal BNRs were found to be strictly dependent upon the nature of oxygen functions in the 2-aryl substituent.

In the literature azaazulene skeletons including benzene ring-fused ones have been generally prepared by cyclization of the corresponding troponoids.[27] On the other hand, it has been reported that Wittig reaction of *N*-methylanilides of α-keto acids with diazomethane derivatives yields 1-azaazulenes by expansion of the benzene ring to a seven-membered ring through alkylidene carbene intermediates.[28] Similar carbene-insertion reactions have been also observed in the rhodium (II)-catalyzed intramolecular Bucher reaction.[29] However, our new 7-5 ring construction reactions should be classified into quite a different reaction category from the reported methods because of S_EAr reactions being controlled by substituents.

On the other hand, azaazulene systems obtained here could be regarded as seven-membered ring-fused indole (or benzindole) equivalents. Therefore, these abnormal BNRs could be replaced by new indole syntheses.[30] In particular they may be useful for the preparation of ervatamine-type indole alkaloids[31] containing a seven-membered ring.

Experimental Section

General. See Suporting Information.

BNR of 4-Methoxy-2-(2-methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphtha-

(25) No azaazulene formation was observed in the BNR of 4,5-dimethoxy-2-hydroxyphenylethyl-*N*-methylformamide, an aliphatic formamide.

(26) Experimental details will be reported elsewhere.

(27) (a) Nishiwaki, T.; Abe, N. *Heterocycles* **1981**, *15*, 547−582. (b) Takayashu, T.; Nitta, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 687−692.

(28) (a) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 4087−4089. (b) Shioiri, T.; Aoyama, T. *J. Synth. Org. Chem. Jpn* **1996**, *54*, 918−928. (c) Horwell, D. C.; McKiernan, M. J.; Osborne, S. *Tetrahedron Lett.* **1998**, *39*, 8729−8732.

(29) (a) Manitto, P.; Monti, D.; Speranza, G. *J. Org. Chem.* **1995**, *60*, 484−485. (b) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4067−4075. (c) Maguire, A. R.; Buckley, N. R.; O'leary, P.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4077−4091.

(30) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075.

(31) (a) Joule, J. A. Indoles, The Monoterpenoid Indole Alkaloids (Saxton, J. E., Ed.). In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1983; Vol 25, part 4, pp 232−239. Alvarez, M.; Joule, J. Monoterpenoid Indole Alkaloids (Saxton, J. E., Ed.). In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol 25, Supplement to Part 4, pp 234−236. (b) Clivio. P.; Richard, B.; Nuzillard, J.-M.; Zeches-Hanrot, M. *Phytochemistry* **1995**, *40*, 987−990.

lene (6). (i) Followed by $NaBH_4$ Reduction: Isolation of 5-Methoxy-2,3-(1-methoxy-8-oxabicyclo[3.2.1]octeno)-1-methyl-7,8-methylenedioxybenz[*g*]indole (10). A solution of **6** (30 mg, 0.073 mmol) in $POCl_3$ (0.5 mL, 5.36 mmol) was stirred at 80 °C for 4 h. After evaporation of the $POCl_3$, the residue was dissolved in MeOH (3.0 mL), and then a large excess of $NaBH_4$ (50 mg, 1.22 mmol) was added. The whole was stirred at room temperature for 2 h. After workup purification of the residue by preparative TLC (hexane:EtOAc = 3:1) gave dihydromacarpine[7] (**9**) (9 mg, 31%) from a less polar fraction and an indole **10** (7 mg, 25%) from a more polar fraction as a light brown solid; ^{1}H NMR (500 MHz) δ 1.64 (1H, m), 2.18 (1H, m), 2.30 (1H, m), 2.40 (1H, m), 2.44 (1H, d, J = 14.9 Hz), 3.36 (1H, dd, J = 14.9, 4.6 Hz), 3.58 (3H, s), 4.00 (6H, s), 4.98 (1H, dif. t, J = 4.6 Hz), 6.05 (2H, fine splitting), 6.99 (1H, s), 7.74 (1H, s), 7.78 (1H, s); HRFABMS m/z 367.1425 (M^+, $C_{21}H_{21}NO_5$ requires m/z 367.1418). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.46; H, 5.69; N, 3.82.

(ii) Isolation of 5,7-Dimethoxy-12-methyl-2,3;9,10-bismethylenedioxy-12-azonianaphth[1,2-*b*]azulene Chloride (8). A solution of **6** (101 mg, 0.247 mmol) in $POCl_3$ (1.0 mL, 10.8 mmol) was stirred at 80 °C for 8 h. After evaporation of the $POCl_3$, fractional recrystallization of the residue from MeOH−EtOH afforded **8** (29 mg, 28%) as dark red needles, mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.09 (3H, s), 4.51 (3H, s), 4.52 (3H, s), 6.31 (2H, s), 6.62 (2H, s), 7.69 (1H, s), 7.82 (1H, s), 7.91 (1H, s), 8.25 (1H, s), 8.68 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.1, 55.6, 59.3, 97.9, 100.0, 100.7, 100.9, 102.4, 103.7, 106.2, 117.0, 117.1, 119.6, 123.5, 131.3, 143.5, 148.0, 148. 5, 151. 6, 152.9, 161.3, 169.9; HRFABMS m/z 392.1131 (M^+, $C_{22}H_{18}NO_6$ requires m/z 392.1134). Anal. Calcd for $C_{22}H_{18}ClNO_6$ $2H_2O$: C, 56.95; H, 4.78; N, 3.02. Found: C, 56.93; H, 4.54; N, 3.02. A mixture of **8** (15 mg, 0.04 mmol) and $NaBH_4$ (10 mg, 0.273 mmol) in MeOH (1.5 mL) was stirred at room temperature for 1.5 h, and workup yielded **10** (10 mg, 75%).

BNR of 2-(2-Isopropoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (11: $R_1 = {}^i$Pr; $R_2 = -CH_2-$): 7-Isopropoxy-12-methyl-2,3;9,10-bismethylenedioxy-12-azonianaphth[1.2-*b*]azulene Chloride (14) and 10-Isopropoxysanguinarine Chloride (15). 11 ($R_1 = {}^i$Pr; $R_2 = -CH_2-$) (500 mg, 1.23 mmol) and $POCl_3$ (2.4 mL, 25.8 mmol) were reacted for 8 h. After washing with Et_2O, fractional recrystallization of the residue from MeOH afforded **14** (111 mg, 21%) as light orange needles, mp >300 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 1.76 (6H, d, J = 6.0 Hz), 4.34 (3H, s), 5.46 (1H, septet, J = 6.0 Hz), 6.22 (2H, s), 6.54 (2H, s), 7.35 (1H, s), 7.69 (1H, d, J = 8.8 Hz), 7.85 (1H, s), 7.93 (1H, s), 8.24 (1H, s), 8.47 (1H, d, J = 8.8 Hz); HRFABMS m/z 390.1345 (M^+, $C_{23}H_{20}NO_5$ requires m/z 390.1341). Anal. Calcd for $C_{23}H_{20}Cl\ NO_5$ $3H_2O$: C, 57.56; H, 5.46; N, 2.92. Found: C, 57.58; H, 5.23; N, 2.97. Treatment of **14** (21 mg, 0.05 mmol) in MeOH (2.0 mL) with $NaBH_4$ (12 mg, 0.329 mmol) for 1.5 h gave **13** ($R_1 = {}^i$Pr) (14 mg, 75%).

On the other hand evaporation of the mother liquor followed by recrystallization from EtOH−Et_2O gave **15** (183 mg, 35%) as dark red needles, mp 253−259 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.45 (6H, d, J = 10.0 Hz), 4.81(3H, s), 5.01 (1H, septet, J = 10.0 Hz), 6.31 (2H, s), 6.54 (2H, s), 7.68 (1H, s), 8.00 (1H, s), 8.13 (1H, s), 8.20 (1H, d, J = 10.0 Hz), 9.48 (1H, d, J = 10.0 Hz), 10.00 (1H, s); HRFABMS m/z 390.1368 (M^+, $C_{23}H_{20}NO_5$ requires m/z 390.1341). Treatment of **15** (20 mg, 0.05 mmol) in MeOH (1.5 mL) with $NaBH_4$ (11 mg, 0.283 mmol) for 1 h gave **12** ($R_1 = {}^i$Pr; $R_2 = -CH_2-$) (14 mg, 83%).

BNR of 2-(4,5-Dimethoxy-2-hydroxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (Isoarnottianamide) (16): 8,9-Dimethoxy-12-methyl-2,3-methylenedioxy-12-azaazulen-11-one (17B). A mixture of **16** (300 mg, 0.79 mmol) and $POCl_3$ (1.2 mL, 13 mmol) in MeCN (50 mL) was stirred at 80 °C for 1 h. The reaction mixture was made alkaline with 5% NH_4OH and extracted with $CHCl_3$. After workup, purification of the crude product by SiO_2 column chromatography ($CHCl_3$) followed by washing with MeOH afforded **17B** (285 mg, quant) as yellow needles, mp 283−285 °C, which were recrystallized from $CHCl_3$−MeOH; ^{1}H NMR (500 MHz) δ 3.96 (3H, s), 4.04 (3H, s), 4.74 (3H, s), 6.12 (2H, s), 6.74 (1H, s), 7.32 (1H, s), 7.35 (1H, s), 7.52 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J = 8.8 Hz), 8.03 (1H, s); ^{13}C NMR (125 MHz) δ 37.4, 56.0, 56.4, 100.8, 101.5, 104.1, 106.4, 115.2, 116.3, 118.4, 120.2, 121.5, 122.2, 131.2, 135.7, 136.8, 147.0, 147.5, 149.9, 157.7, 176.5; HRFABMS m/z 364.1183 (M + H^+, $C_{21}H_{18}NO_5$ requires 364.1185). Anal. Calcd for $C_{21}H_{17}NO_5$ $1/2H_2O$: C, 67.73; H, 4.87; N, 3.76. Found: C, 67.80; H, 4.85; N, 3.73.

BNR of 2-(4,5-Dimethoxy-2-hydroxyphenyl)-*N*-methylformanilide (20a) under Various Conditions. (i) At Room Temperature with Aqueous Workup: 6,7-Dimethoxy-10-methylbenz[*b*]azaazulen-9-one (21) and 7-Chloro-6-methoxy-10-methylbenz[*b*]azaazulen-9-one (23). A solution of **20a** (11 mg, 0.038 mmol) in $POCl_3$ (0.4 mL, 3.97 mmol) was stirred at room temperature for 3 days. The reaction mixture was evaporated and extracted with $CHCl_3$. After workup, purification of the crude product by preparative TLC ($CHCl_3$:MeOH = 30:1) afforded **21** (6 mg, 63%) as yellow fine prisms, mp 223−224 °C; IR (Nujol) ν_{max} 1559 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.96 (3H, s), 4.02 (3H, s), 4.40 (3H, s), 6.75 (1H, s), 7.33 (1H, dt, J = 8.0, 1.2 Hz), 7.39 (1H, s), 7.53 (1H, dif d, J = 8.0 Hz), 7.55 (1H, dt, J = 8.0, 1.0, 1.2 Hz), 8.03 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz) δ 33.0, 56.0, 56.5, 104.7, 110.5, 115.2, 119.1, 120.0, 120.8, 125.1, 127.2, 135.8, 140.1, 149.4, 158.1, 177.0; HRFABMS m/z 270.1119 (M + H^+, $C_{16}H_{16}NO_3$ requires m/z 270.1130). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.27; H, 5.63; N, 4.85 and **23** (2 mg, 15%), which was identical with the sample obtained from the reaction at 50 °C mentioned below.

(ii) At 50°C with Aqueous Workup: 7-Chloroazaazulenone 23. A solution of **20a** (51 mg, 0.176 mmol) in $POCl_3$ (0.8 mL, 8.6 mmol) was stirred at 50 °C for 3 h. The reaction mixture was evaporated and extracted with $CHCl_3$ containing a small amount of MeOH. After workup, the crude product was recrystallized from MeOH−$CHCl_3$ to afford **23** (41 mg, 85%) as yellow prisms, mp 209−212.5 °C; IR (Nujol) ν_{max} 1654 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.07 (3H, s), 4.27 (3H, s), 7.37 (1H, ddd, J = 10.0, 10.0, 1.2 Hz), 7.51 (1H, d, J = 10.0 Hz), 7.58 (1H, ddd, J = 10.0, 10.0, 1.2 Hz), 7.59 (1H, s), 7.64 (1H, s), 8.02 (1H, d, J = 10.0 Hz); ^{13}C NMR (100 MHz) δ 35.0, 56.1, 107.2, 110.6, 119.5, 120.2, 121.6, 125.0, 127.7, 133.6, 134.2, 134.7, 140.8, 157.0, 176.7; HRFABMS m/z 274.0636 (M^+, $C_{15}H_{13}ClNO_2$ requires m/z 274.0635) and 276.0615 (M^+ + 2, $C_{15}H_{13}ClNO_2$ requires m/z 276.0606). Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.66; H, 4.33; N, 5.08.

(iii) At 50°C without Aqueous Workup: 9-Chloro-6,7-dimethoxy-10-methyl-10-azoniabenz[*b*]azulene Chloride (25). A solution of **20a** (50 mg, 0.17 mmol) in $POCl_3$ (0.8 mL, 8.6 mmol) was stirred at 50 °C for 2 h. After evaporation washing the residue with Et_2O afforded **25** (58 mg, quant) as a yellow solid, mp 157−159 °C, which was slowly liquefied; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ 4.32 (3H, s), 4.38 (3H, s), 4.54 (3H, s), 7.51 (1H, s), 7.66 (1H, t, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 7.99 (1H, t, J = 8.0 Hz), 8.65 (1H, d, J = 8.0 Hz), 9.02 (1H, s); HRFABMS m/z 288.0786 (M^+, $C_{15}H_{15}ClNO_2$ requires m/z 288.0791) and 290.0736 (M^+ + 2, $C_{15}H_{15}ClNO_2$ requires m/z 290.0791).

9*H*-6,7-Dimethoxy-10-methylbenz[*b*]azaazulene (22). A mixture of **21** (111 mg, 0.41 mmol) and $LiAlH_4$ (47 mg, 1.22 mmol) in THF (19 mL) was refluxed for 1 h. After addition of water and 20% NaOH, precipitates were removed by filtration through Celite and washing with EtOAc and MeOH. The filtrate was evaporated and purified by SiO_2 column chromatography (hexane:EtOAc = 5:1) to give **22** (56 mg, 53%) as colorless prisms, mp 163−166 °C; ^{1}H NMR (400 MHz) δ 3.14 (2H, d, J = 7.6 Hz), 3.59 (3H, s), 3.74 (3H, s), 3.87 (3H, s), 4.89 (1H, t, J = 7.6 Hz), 6.55 (1H, s), 7.13 (1H, dt, J = 7.6, 1.1 Hz), 7.19 (1H, dt, J = 7.6, 1.1 Hz), 7.28 (1H, d, J = 7.6 Hz), 7.60 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz) δ 20.3, 29.5, 55.8, 55.9, 94.7, 100.4, 108.7, 109.4, 117.6, 119.6, 121.0, 126.0, 135.2, 137.3, 149.9, 152.8; HRFABMS m/z 255.1252 (M^+, $C_{16}H_{17}NO_2$ requires m/z 255.1259).

6-Methoxy-10-methylbenz[*b*]azaazulen-9-one (24). A mixture of **23** (50 mg, 0.18 mmol) and $NaBH_4$ (83 mg, 2.2 mmol) in MeOH (13 mL) was stirred at room temperature for 1.5 h and extracted with $CHCl_3$. After workup, purification of the crude product by preparative TLC (hexane:EtOAc = 2:1) afforded **24** (56 mg, 53%) as colorless prisms, mp 159−160 °C; ^{1}H NMR (400 MHz) δ 3.93 (3H, s), 4.39 (3H, s), 7.16 (1H, s), 7.16 (1H, d, J = 1.0 Hz), 7.32 (1H, dt, J = 8.3, 1.0 Hz), 7.34 (1H, dif s), 7.51 (1H, d, J = 8.3 Hz), 7.56 (1H, dt, J = 8.3, 1.0 Hz), 8.06 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz) δ 33.6, 55.5, 104.4, 110.4, 120.5, 120.8, 123.1, 125.0, 127.7, 131.8, 136.8, 136.8, 140.4, 155.3, 178.4; HRFABMS *m*/*z* 240.1010 ($M + H^+$, $C_{15}H_{14}NO_2$ requires *m*/*z* 240.1025). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.86. Found: C, 74.91; H, 5.36; N, 5.71.

BNR of 2-(3,6-Dimethoxy-2-hydroxyphenyl)-*N*-methylformanilide (20h): 5-Formyl-3-methoxy-6-[3-(1-methylindoyl)]-2*H*-pyran-2-one (29). A solution of **20h** (202 mg, 0.702 mmol) in $POCl_3$ (3.2 mL, 34.3 mmol) was stirred at 50 °C for 4 h. The reaction mixture was evaporated, poured into water, and extracted with $CHCl_3$. After workup, purification of the crude product by SiO_2 column chromatography (hexane:EtOAc = 1:1) afforded **29** (38 mg, 19%) as yellow prisms, mp 205−209 °C; IR (Nujol) ν_{max} 1741, 1664 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.92 (6H, s), 7.11 (1H, s), 7.31 (1H, dd, J = 8.0, 1.2 Hz), 7.38 (1H, dd, J = 8.0, 1.2 Hz), 7.42 (1H, d. J = 8.0 Hz), 7.49 (1H, s), 7.95 (1H, d, J = 8.0 Hz), 9.92 (1H, s); ^{13}C NMR (125 MHz) δ 33.6, 56.4, 105.2, 110.08, 110.13, 114.3, 120.7, 122.4, 123.9, 126.1, 133.2, 137.3, 142.9, 157.6, 160.8, 187.7; HRFABMS *m*/*z* 284.0927 ($M + H^+$, $C_{16}H_{14}NO_4$ requires *m*/*z* 284.0923). A deformylated product **30** (34 mg, 19%) was also obtained with recovery of **20h** (59 mg, 29%).

Supporting Information Available: Preparation method and spectral data of the starting aromatic formamides for BNR [**11** (R_1 = ^{i}Pr; R_2 = Me or R_2 = $-CH_2-$) and **16**, **20a**−**g**, and **20h**], reaction conditions of BNRs in Table 1 and **20b** without aqueous workup, and the spectral data of products obtained, ^{1}H NMR charts of **13** (R = H), **15**, **22**, **25**, **26**, and **29**, and X-ray data of **22** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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