Development of a Novel Indole Synthesis and Its Application to Natural Products Synthesis

Yoshihisa Kobayashi and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, CREST, The Japan Science and Technology Corporation (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

J. Heterocyclic Chem., **35**, 1043 (1998).

Synthesis of 3-Monosubstituted and 2,3-Disubstituted Indoles.

Indole is ubiquitous among a wide range of natural products. While a large number of preeminent methods have already been well documented for the construction of this important nucleus, there appear to be few practical procedures available for the synthesis of 2,3-disubstituted indoles [1]. Herein we discuss a versatile tin-mediated indole synthesis, which is particularly suited for the preparation of 2,3-disubstituted indoles, and its application to the synthesis of some natural products. In addition, a novel amine synthesis, which we discovered during the course of the synthetic studies of indole alkaloids, is also discussed.

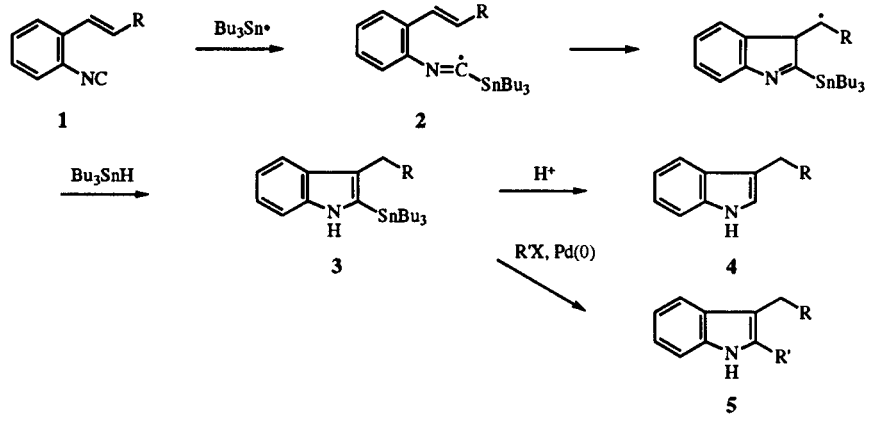
It has been known for quite some time that tin radicals add to isonitriles to form imidoyl radicals [2]. Despite the fact that some of the imidoyl radicals have been demonstrated to have strong synthetic potentials for inter- and intramolecular carbon-carbon bond formation [3], simple α-stannoimidoyl radicals have attracted little attention among synthetic organic chemists. At the outset of this research, we reasoned that the α-stannoimidoyl radical **2**, generated from *o*-isocyanostyrene derivative **1** by addition of a tri-*n*-butyltin radical, should lead to the formation of the 2-stannylindole **3** through a radical cyclization and the subsequent tautomerization as illustrated in Scheme 1. The 2-stannylindole **3** would in turn be an ideal precursor for 3-substituted indole **4** or 2,3-disubstituted indole **5**.

Treatment of the isonitriles **1** [4] with tributyltin hydride and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) indeed gave the desired 3-substituted indoles **4** in high yields upon acidic workup as shown in Table 1 [5]. It should be noted that the substrates bearing radical-stabilizing substituents at the β-position gave excellent yields (entries 1 and 4). While a substantial amount (33%) of the tetrahydroisoquinoline **6** was formed from the *E*-substrate **1e** (entry 5), the problem could be alleviated by employing the Z-substrate **1f** (entry 6).

The success of the foregoing experiments engendered cautious optimism concerning the synthetic versatility of the radical-induced indole formation. At this juncture, however, we realized that a more versatile method needed to be developed for preparation of the requisite *o*-isocyanostyrene derivatives. To this end, we focused our attention on the development of suitable Wittig or Horner-Wadsworth-Emmons reagents such as **10** as the constituents of the benzene portion of the indoles. These reagents would then be condensed with a variety of aldehydes, resulting in the formation of the styrenes **1**.

The crucial S_NAr reaction was initiated by adding 1-fluoro-2-nitrobenzene **7** to a mixture of triethyl phosphonoacetate and potassium hydride (Scheme 2). The resultant substitution product **8** was quantitatively converted to **9** upon basic hydrolysis and the simultaneous decarboxylation. Subsequent catalytic hydrogenation of the nitro group followed by formylation of the resultant amine with acetic formic anhydride furnished the formamide. Upon treatment with phosgene and triethylamine, the formamide underwent smooth dehydration to give the desired isonitrile **10** in excellent yield.

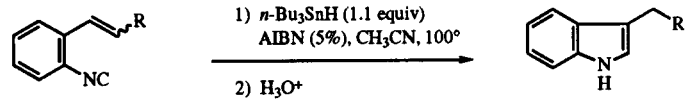
Scheme 1



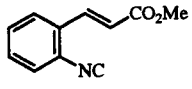
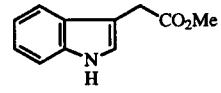
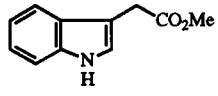
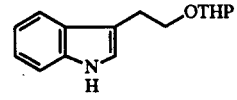
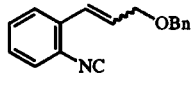
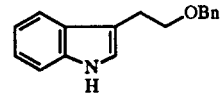
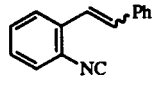
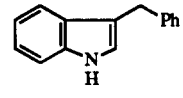
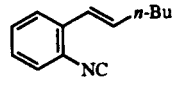
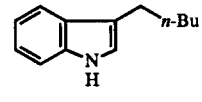
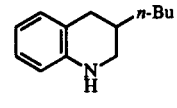
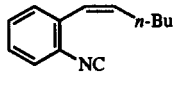
1 **2** **3** **4** **5**

Table 1

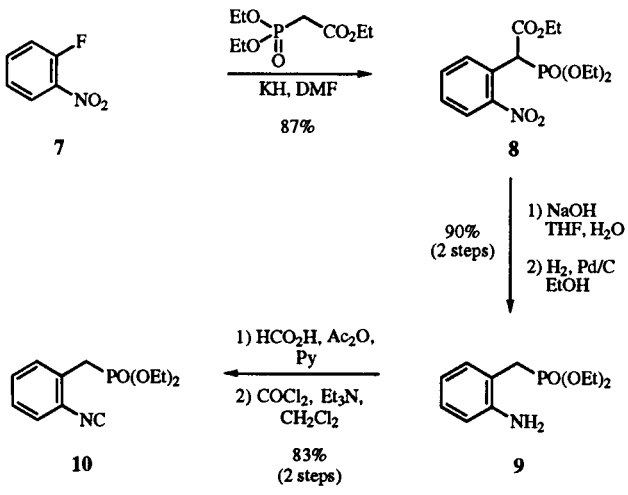
Synthesis of 3-Substituted Indoles



1 **4**

Entry	Substrate	Product	Isolated yield, %
1	 **1a**	 **4a**	91
2	 **4a**	 **4b**	83
3	 **1c** (*E*/*Z* 6:1)	 **4c**	68
4	 **1d** (*E*/*Z* 7:2)	 **4d**	83
5	 **1e**	 **4e**	51
		 **6**	33
6	 **1f**	**4e**	72
		6	18

Scheme 2

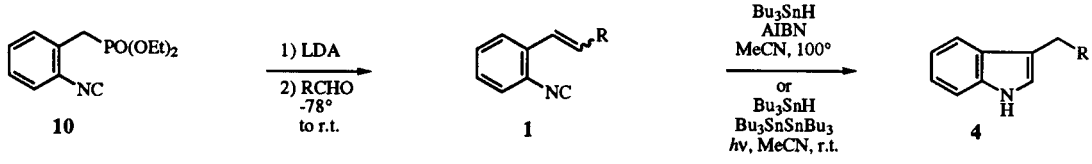


The Horner-Wadsworth-Emmons reagent **10** was condensed with several aldehydes under the standard conditions (lithium diisopropylamide, tetrahydrofuran) to furnish the expected olefins in excellent yields. Table 2 summarizes representative examples and demonstrates that a wide range of *o*-isocyanostyrenes are available through this new procedure. With the indole precursors securely in hand, we were ready to test the generality of our radical-induced indole synthesis. Submission of the above substrates to the aforementioned conditions (tributyltin hydride and 2,2'-azobisisobutyronitrile in acetonitrile) resulted in the clear-cut formation of the corresponding indoles.

The important ramification of the above finding is that the hitherto unknown, *N*-unprotected 2-stannylindoles **3** have become readily available for further manipulation. To the best of our knowledge, the chemistry of 2-stannylindole has not been developed extensively presumably because metallation of the *N*-protected indole has been the only practical method for synthesizing it [6,7]. Since 2-stannylindoles **3** were prone to undergo facile destannylation during workup, Stille's palladium-mediated coupling [8] was performed on the crude reaction mixture immediately after the completion of the indole synthesis. As expected, the one-pot Stille coupling proceeded smoothly to give the desired 2,3-disubstituted indoles **5** in 49-82% yield as shown in Table 3. A few comments are worthy of note. Bromobenzene offered a higher yield of the coupling product **5a** than iodobenzene did (Table 3, entries 1 and 2). As reported by Stille [8c], addition of lithium chloride

Table 2

Synthesis of 3-Substituted Indoles



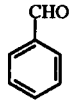
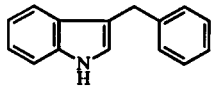
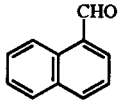
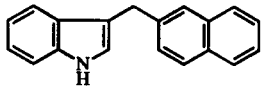
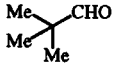
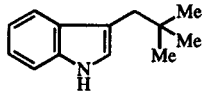
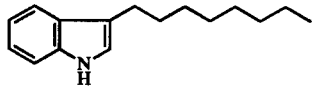
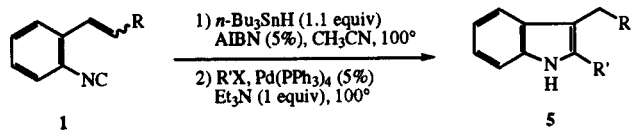
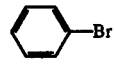
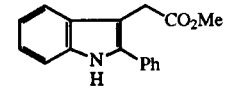
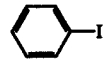
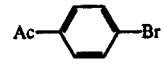
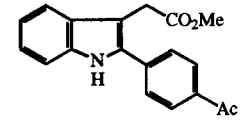
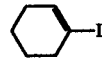
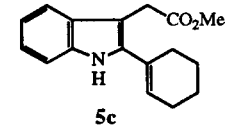
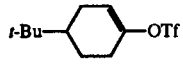
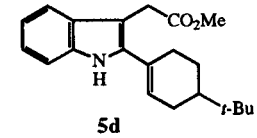
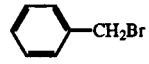
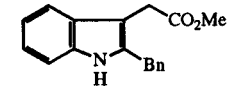
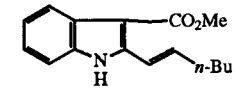
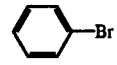
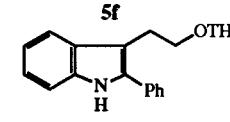
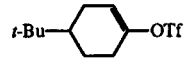
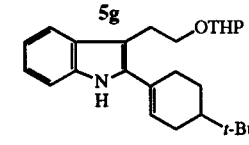
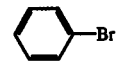
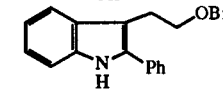
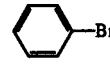
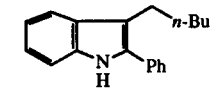
RCHO	Yield, %	Product	Yield, %
	90%	 **4f**	85%
	91%	 **4g**	86%
	93%	 **4h**	77%
	91%	 **4i**	82%

Table 3

One-pot Synthesis of 2,3-Disubstituted Indoles



1 5

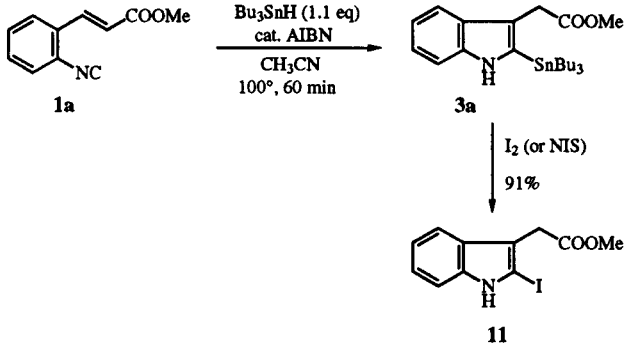
Entry	Substrate	R'X	Equivalent	Time (hours)	Product	Yield, %
1	**1a**		1.2	5		82
2	**1a**		1.2	8	**5a**	68
3	**1a**		1.2	12		81
4	**1a**		1.2	3	**5b**	75 [a]
5	**1a**		3.0	8	 **5c**	58
6	**1a**		3.0	7	 **5d**	64
7	**1a**		3.0	1	 **5e**	71 [b]
8	**1a**		3.0	8	 **5f**	71 [c]
9	**1b**		3.0	11	 **5g**	63
10	**1b**		3.0	7	 **5h**	49 [a]
11	**1c**		3.0	10	 **5i**	60
12	**1f**		3.0	8	 **5j**	65

[a] LiCl (5 equiv) and 10% volume of DMF were added; [b] No Et_3N was added; [c] CuI (1 equiv) was added.

was essential for successful couplings with triflates (entries 4, 6, and 10). The 2-benzylindole **5e** was readily obtained by treatment with benzyl bromide (entry 7). When *trans*-1-iodohexene was used as a coupling partner, addition of 1 equivalent of cuprous iodide was needed to suppress the formation of the undesired 2-(1-butyletheny)indole (entry 8) [9].

The significance of this one-pot synthesis of a 2,3-disubstituted indole is not limited to the Stille coupling with 2-stannylindoles. Since the tin-carbon bond can be readily oxidized with iodine, we envisioned that this method would pave the way for the synthesis of a range of *N*-unprotected 2-iodoindoles (Scheme 3). Since there are not many practical procedures reported in the literature for the preparation of *N*-unprotected 2-iodoindoles, its chemistry has not yet been explored extensively.

Scheme 3



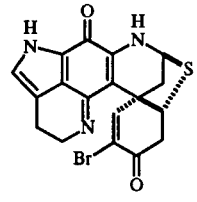
Our newly developed methodology makes not only those 2-iodoindole derivatives more readily accessible, but also extends the versatility of the coupling partners. In addition to aryl halides, vinyl iodides, vinyl triflates, and benzyl bromides which are suitable for the one-pot Stille coupling reactions with 2-stannylindoles, we can now include acetylenes (Sonogashira coupling), acrylates (Heck reaction), and vinyl tin reagents (Stille coupling) for couplings with 2-iodoindoles (Scheme 4).

Since a wide variety of functional groups are known to tolerate both radical and palladium-mediated reactions, our efficient synthesis is well suited for a facile construction of a range of 3- or 2,3-substituted indoles from readily accessible isonitriles.

Synthetic Approach to Discorhabdin A.

Much attention has been focused upon isolation and structure determination of biologically active materials from marine sources. One of the most interesting classes of these compounds is the structurally diverse group of alkaloids containing the pyrrolo[4,3,2-*de*]quinoline nucleus. Representative examples include the discorhabdins [10].

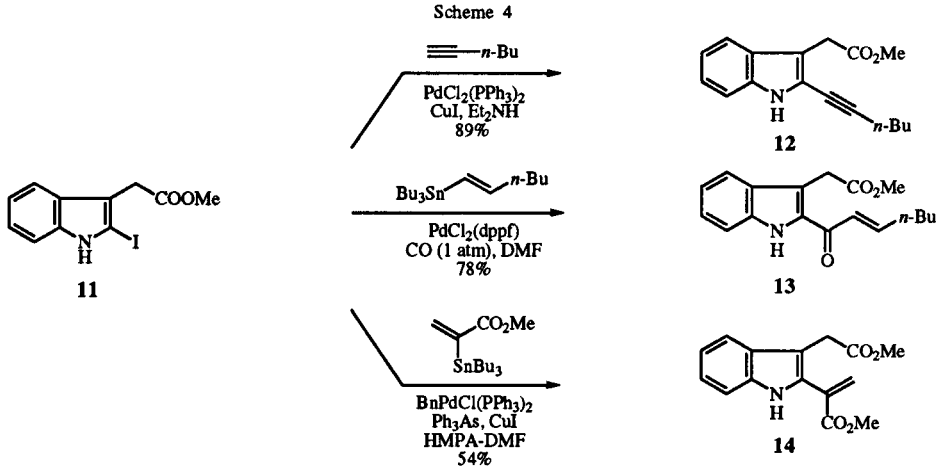
In order to apply this newly developed indole synthesis to total synthesis of indole alkaloids, we started our synthetic approaches toward the total synthesis of Discorhabdin A which was isolated by Perry and coworkers from the sponge of *Latrunculia* du Bocage in New Zealand (Figure 1) [11].



Discorhabdin A

Figure 1.

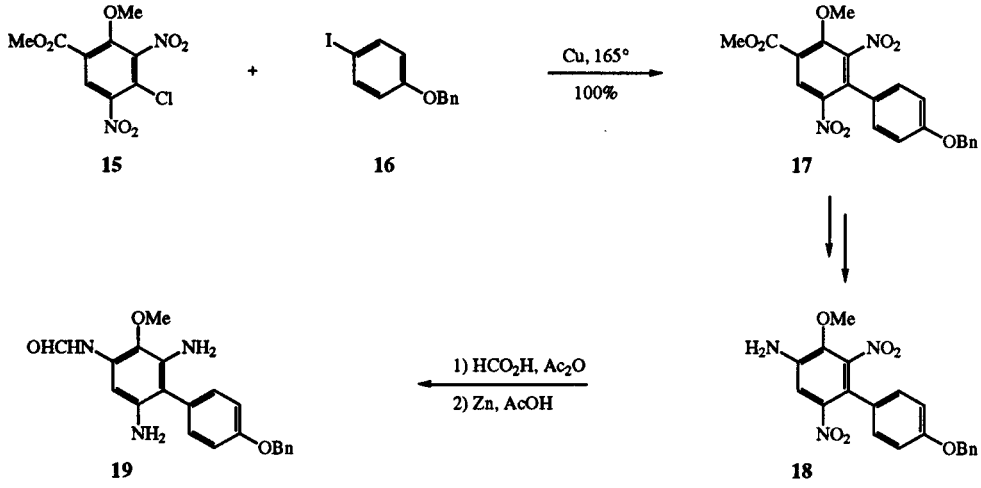
Scheme 4



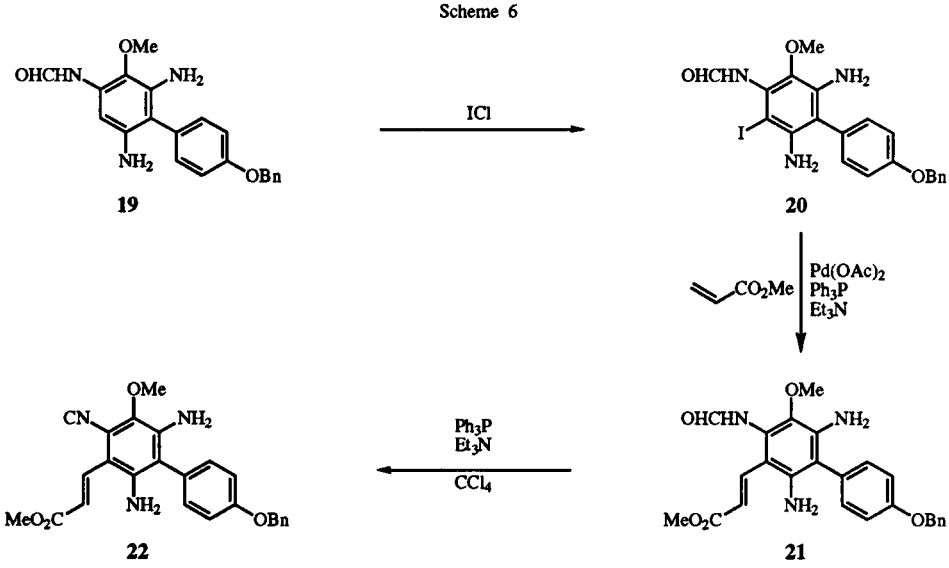
When heated with *p*-benzyloxyiodobenzene **16** in the presence of copper powder, nitro chloride **15** underwent a facile Ullmann reaction to give **17** in a quantitative yield (Scheme 5). Alkaline hydrolysis of the methyl ester in **17** followed by the Curtius rearrangement of the resultant acid furnished dinitroamine **18**. With the dinitroamine in hand, we then focused our attention on the indole formation using our tin-mediated radical cyclization. Since the nitro groups might interfere with the radical chain reaction, it was determined that the indole formation would be carried out after reduction of the nitro groups. To this end, the free amino group was first converted into a formamide using the mixed anhydride conditions. Subsequent reduction of the nitro groups with activated zinc dust gave the desired diamine **19**.

Iodination of the electron-rich aromatic compound **19** was performed by means of iodine monochloride, giving the diamino iodide **20** in nearly 80% yield (Scheme 6). The precursor for the indole synthesis, **21**, could be prepared through the Heck reaction of iodide **20** with methyl acrylate followed by dehydration of the formamide using triphenylphosphine, carbon tetrachloride and triethylamine. It should be noted that dehydration of the formamide was successful in the presence of the reactive diamines under the reaction conditions.

Scheme 5

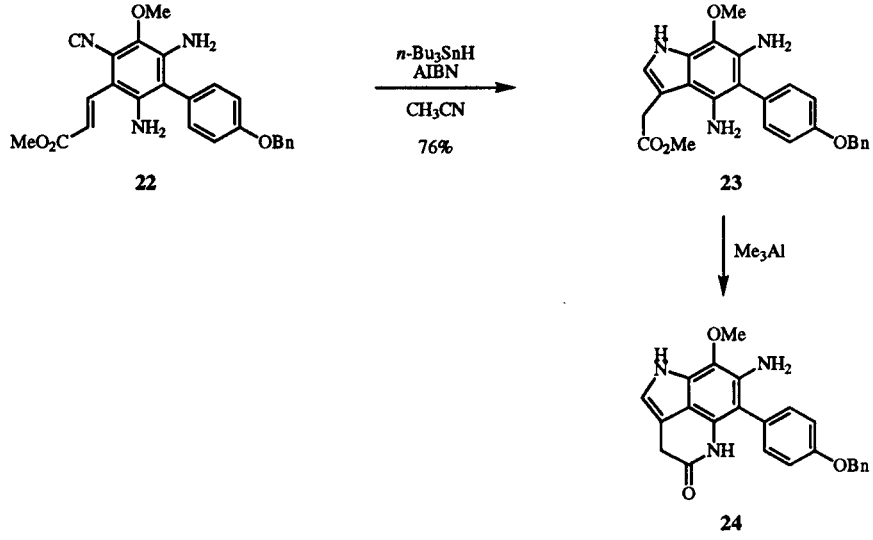


Scheme 6



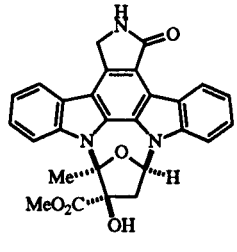
Radical cyclization proceeded smoothly when isonitrile **22** was heated with tributyltin hydride and 2,2'-azobisisobutyronitrile in acetonitrile, providing the somewhat unstable diaminoindole **23** in 76% yield (Scheme 7). The lactam **24** was obtained from diaminoindole **23** by treatment with trimethylaluminum. The successful conversion of the fully substituted aromatic isonitrile **22** to the indole **23** demonstrates the versatility of our methodology.

Scheme 7



Synthetic Studies on (+)-K252a.

Indolocarbazole alkaloid (+)-K252a (Figure 2), isolated by Kase and coworkers [12] at Kyowa Hakko in 1986, has a strong PKC inhibitory activity. The first total synthesis of (+)-K252a has recently been reported by Wood and coworkers [13].

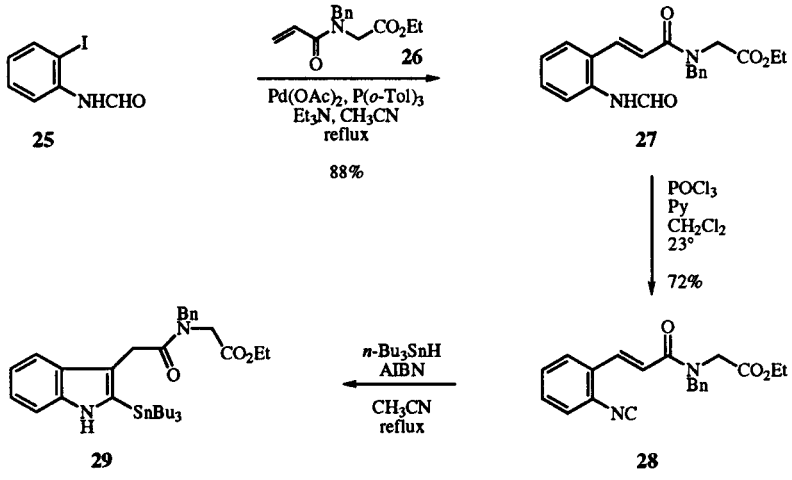


(+)-K252a

Figure 2.

Heck reaction of the readily available *o*-iodoformanilide **25** with acrylamide **26** gave cinnamamide **27** which was subjected to dehydration with phosphoryl chloride to afford *o*-isocyanocinnamamide **28** (Scheme 8). Radical-mediated cyclization of **28** was effected by heating with tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile in acetonitrile at 90° to give the unstable 2-stannylindole **29**.

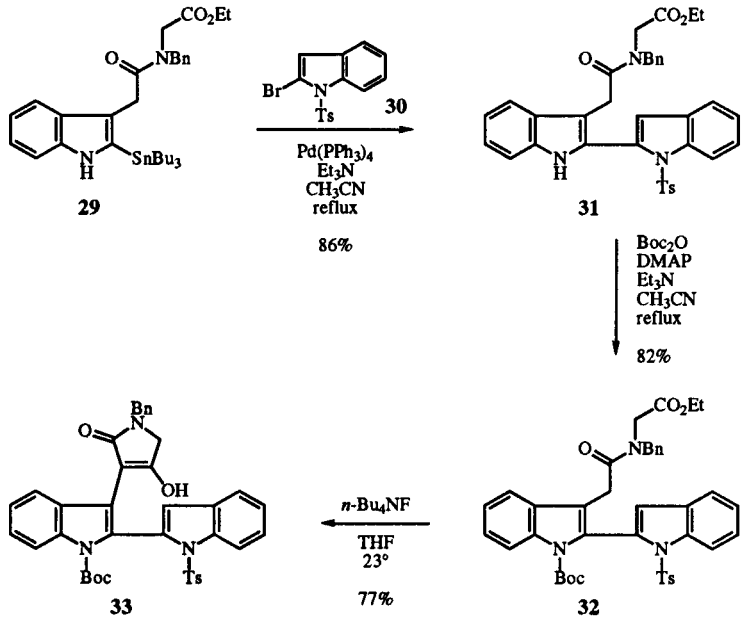
Scheme 8



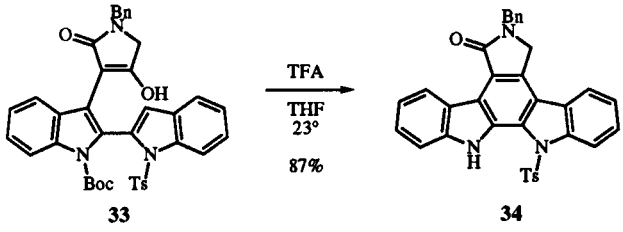
Since the 2-stannylindole **29** was too unstable to isolate, the subsequent Stille coupling with *N*-protected 2-bromoindole **30** was performed in a one-pot process to give the biindole **31** (Scheme 9). Following protection of the indole nitrogen in **31** as its *t*-butyl carbamate, Dieckmann-type condensation of **32** furnished lactam **33** by employing tetra-*n*-butylammonium fluoride as a base.

Upon treatment with trifluoroacetic acid, **33** underwent simultaneous deprotection of the Boc group and cyclization to give the desired indolocarbazole **34** in high yield (Scheme 10). The regioselective synthesis of the *N*-protected K252a-aglycon moiety has been thus achieved by employing the novel tin-mediated indole synthesis.

Scheme 9



Scheme 10

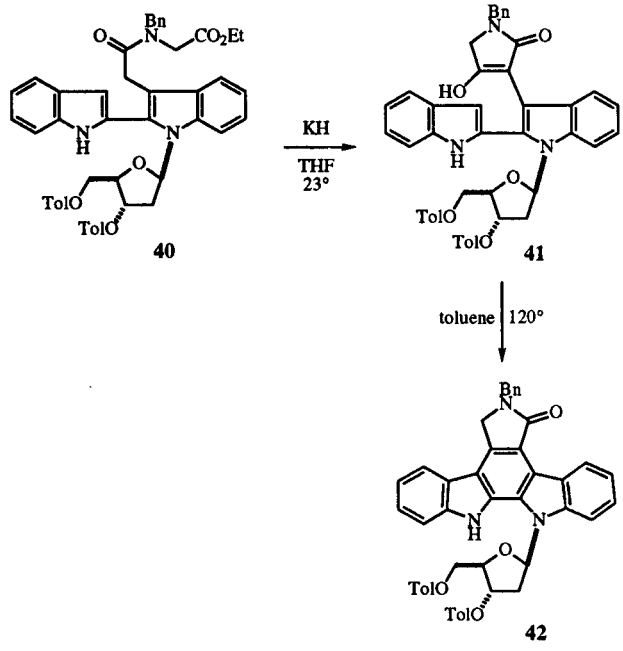


33 34

2-Iodoindole **35**, which was obtained from the 2-stannylindole **29** by treatment with iodine, and *o*-aminophenylacetylene **36** [14] were submitted to the Sonogashira coupling conditions, yielding the 2,3-disubstituted indole **37** (Scheme 11). Stereoselective glycosidation of the indole nitrogen was accomplished by deprotonation of the indole NH in **37** with sodium hydride followed by addition of the deoxyribosyl chloride **38** [15] to give the 1,2,3-trisubstituted indole **39**. Subsequently, **39** was subjected to palladium-mediated cyclization using a catalytic amount of $PdCl_2(CH_3CN)_2$, giving the desired biindole **40** in a quantitative yield.

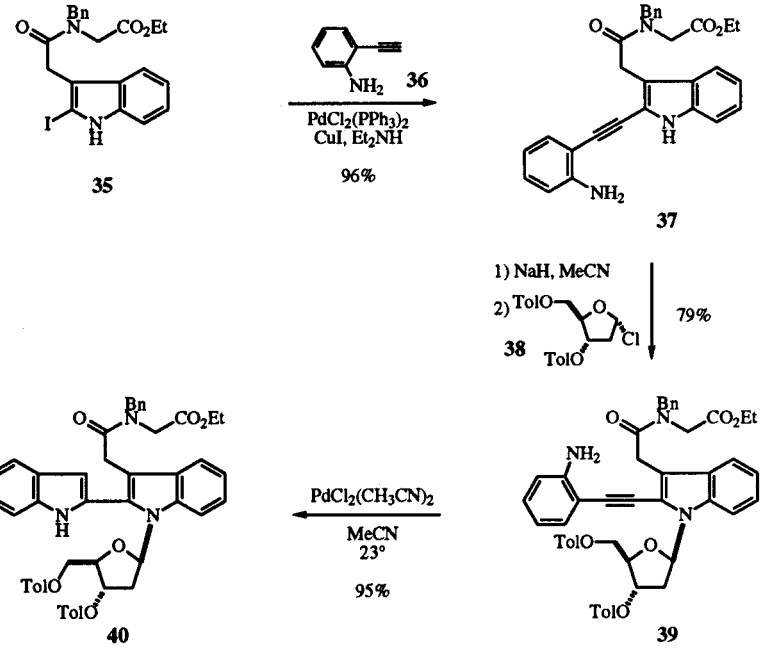
The biindole **40**, upon treatment with potassium hydride, furnished the cyclization product **41**, which underwent electrocyclic ring closure when heated in toluene, giving the desired indolocarbazole **42** as a result of spontaneous dehydration (Scheme 12). The indolocarbazole **42** is an important intermediate for the regioselective synthesis of (+)-K252a which is currently underway.

Scheme 12



40 41 42

Scheme 11

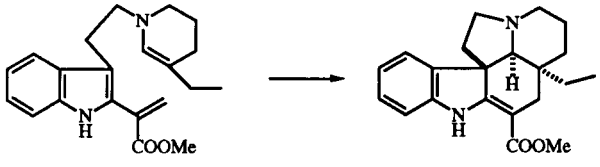


35 37 39 40

Synthetic Studies on (±)-Vincadifformine.

As a prime representative of *aspidosperma* alkaloids, vincadifformine (**44**) occurs in both enantiomeric as well as racemic forms in nature. Being an important member of the pentacyclic skeleton of *aspidosperma/iboga* series of indole alkaloids, vincadifformine has been synthesized several times in the past twenty years [16]. Kuehne's total synthesis of vincadifformine went through secodine (**43**), a biomimetic intermediate postulated by Wenkert and Scott (Scheme 13) [17]. Since our indole synthesis [18] is particularly suited for the synthesis of 2,3-disubstituted indoles such as **43**, we decided to carry out a total synthesis of Vincadifformine to demonstrate the general applicability of our methodology.

Scheme 13

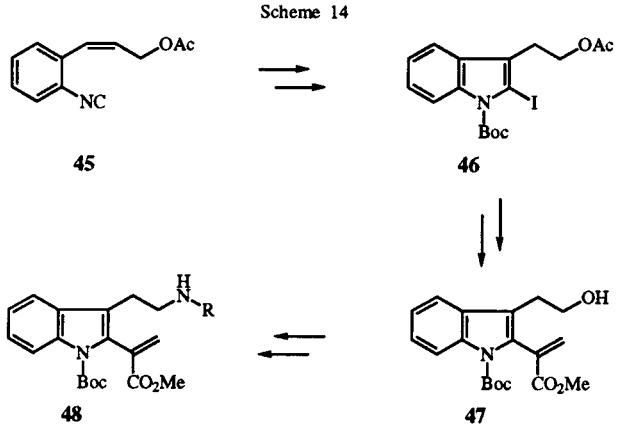


43 **44**

Vincadifformine

Starting from the isonitrile **45**, readily prepared from commercially available *o*-iodoaniline in several steps, 2-iodoindole **46** was obtained by employing our indole synthesis methodology shown above (Scheme 14). The Stille coupling with methyl 2-tri-*n*-butylstannylacrylate and subsequent hydrolysis of the acetate then furnished the alcohol **47**.

Scheme 14



45 **46**

48 **47**

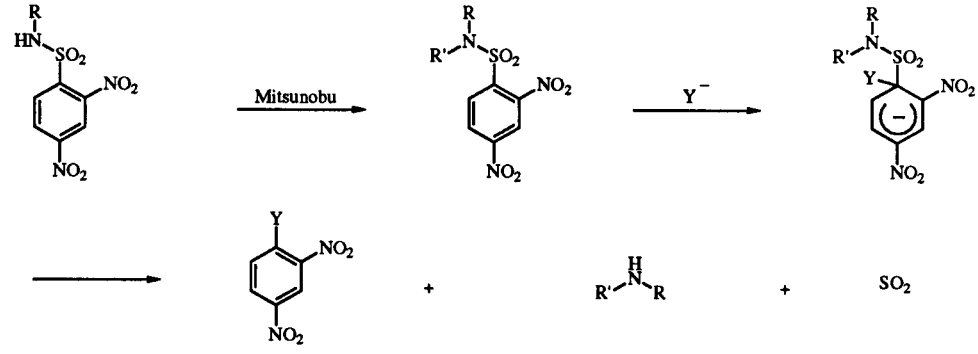
At this juncture, we focused our attention on two of the many available coupling procedures to give the amine **48**: reductive amination of the indole aldehyde, derived from **47** by Swern oxidation, with an amine using $NaBH_3CN$ or Mitsunobu alkylation of **47** with a suitably activated amine derivative. The first protocol was soon ruled out because the indole aldehyde was too unstable to survive the reductive amination. We therefore concentrated on the Mitsunobu alkylation of **47**. The Mitsunobu reaction would be successful only when the nucleophile component is a Brønsted acid with a p*K*a value around 11 or lower [19]. Accordingly, it is imperative that an amine group needs to be activated to be used for the Mitsunobu reaction. Toluenesulfonamides [20] or trifluoroacetamides [21] in the case of aromatic amines have been used for this purpose. However, an unfortunate problem with these methods, especially with sulfonamides, is that relatively harsh conditions are required for their *N*-deprotection. Therefore, it was necessary to create an entirely new protecting group which could meet these requirements. It seemed quite obvious from the outset that the amine had to be protected as a sulfonamide derivative which could be deprotected under very mild conditions. After many attempts, we finally found that 2,4-dinitrobenzenesulfonamides could be cleaved *via* the S_NAr processes as shown in Scheme 15. A facile deprotection of the 2,4-dinitrobenzenesulfonyl group occurs *via* the Meisenheimer complex upon addition of a soft nucleophile such as thiolates, giving the desired secondary amine.

For example, an amine **50** reacted with commercially available 2,4-dinitrobenzenesulfonyl chloride to give sulfonamide **51**. This sulfonamide underwent smooth Mitsunobu coupling with indole alcohol **47** to afford compound **52** in excellent yield as shown in Scheme 16. Application of this novel amine synthesis to a total synthesis of vincadifformine is now in progress.

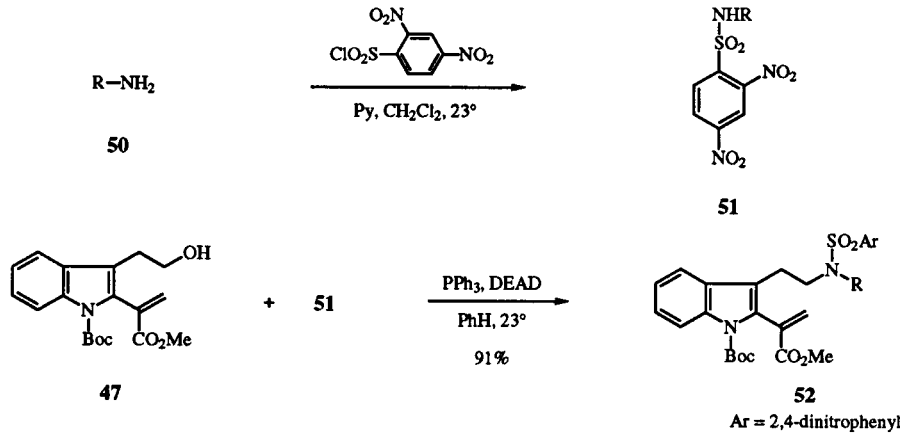
Chemistry of Nitrobenzene Sulfonamides: Preparation of Diamines.

Conversion of primary amines to the corresponding secondary amines appears deceptively simple [22]. Alkylation of primary amines with alkyl halides and sulfonates frequently leads to the formation of the undesired tertiary amines and/or quaternary ammonium salts. Reductive alkylation with aldehydes or ketones using $NaBH_3CN$ often produced tertiary amines to a varying extent unless the desired secondary amine is sterically hindered. Perhaps reduction of *N*-monoalkyl amides with such strong reducing agents as lithium aluminum hydride (LAH), diisobutylaluminum hydride (DIBAL), or borane might be the most reliable procedure. As mentioned above, to circumvent these problems, the Mitsunobu alkylations of toluenesulfonamides and trifluoroaceta-

Scheme 15



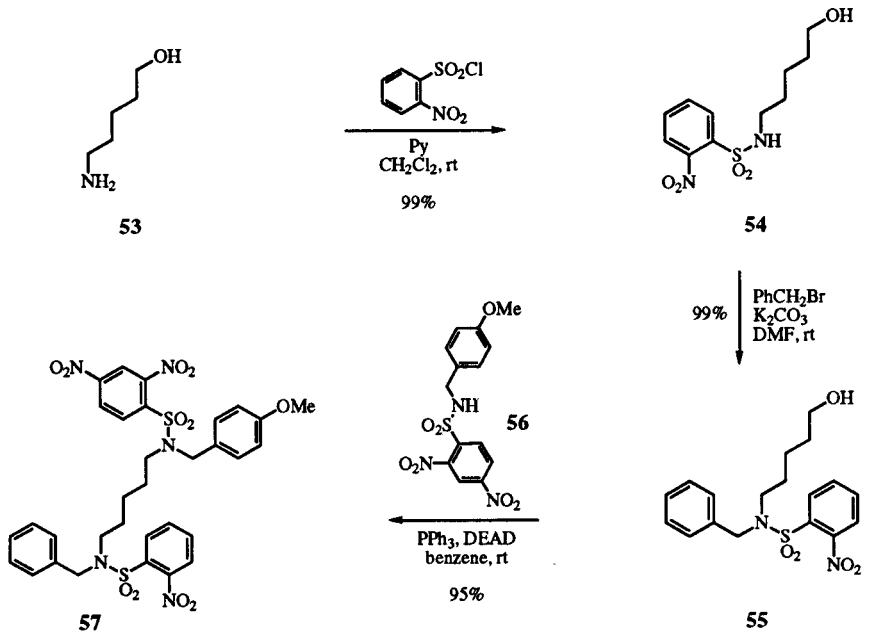
Scheme 16



mides have recently been reported. However, due to the relatively harsh deprotection conditions, these methods do not appear to be suitable for the preparation of the base sensitive secondary amines. 2-Nitro- and 2,4-dinitrobenzenesulfonamides [23,24], which we developed during the course of the total synthesis of vincadifformine, can be applied to the synthesis of a wide range of secondary amines.

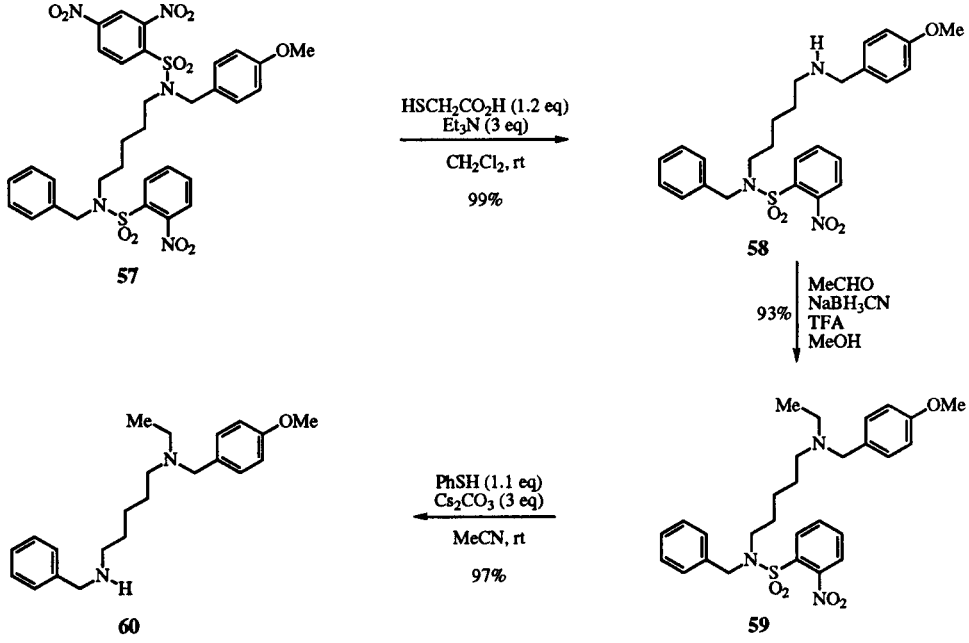
Since both 2-nitro- and 2,4-dinitrobenzenesulfonamides, derived from primary amines, can be easily *N*-alkylated by the Mitsunobu reaction or by the conventional methods, a combination of these sulfonamides may be used for the preparation of a wide variety of diamines as illustrated in Scheme 17. To demonstrate the general applicability of our protocol, 5-amino-1-pentanol (**53**) was chosen as the starting material. Thus, the readily available amino alcohol **53** was converted to 2-nitrobenzenesulfonamide **54** by treatment with 2-nitrobenzenesulfonyl chloride (NsCl) and pyridine in dichloromethane. Selective alkylation of **54** with benzyl bromide and potassium carbonate in dimethylformamide furnished *N,N*-dialkyl-2-nitrobenzenesulfonamide **55** in almost quantitative yield. The second amino functionality was introduced to **55** by means of the Mitsunobu reaction (diethyl azodicarboxylate (DEAD), Ph_3P, benzene) with *N-p*-methoxybenzyl-2,4-dinitrobenzenesulfonamide **56**, which was easily prepared from *p*-methoxybenzylamine and 2,4-dinitrobenzenesulfonyl chloride (DNsCl).

Scheme 17



Selective deprotection of 2,4-dinitrobenzenesulfonamide **57** was performed by treatment with mercaptoacetic acid and triethylamine in dichloromethane to give the desired amine **58** in a quantitative yield (Scheme 18). The secondary amine **58** can either alkylated or acylated at this stage. For example, **58** was subjected to reductive alkylation to give the tertiary amine **59** in high yield. Finally, the 2-nitrobenzenesulfonamide **59** was deprotected with benzenethiol and cesium carbonate in acetonitrile to give the amine **60** in high yield, which, once again, can either be alkylated or acylated with a wide variety of reagents.

Scheme 18



Because of the extreme ease of the entire procedure, we believe that the use of 2,4-dinitrobenzenesulfonamides in conjunction with 2- and 4-nitrobenzenzsulfonamides serves as a method of choice for the preparation of a wide variety of secondary amines just like the Gabriel synthesis for primary amines. As illustrated in Scheme 18, our protocol seems particularly suited for preparation of the combinatorial library of diamine derivatives which may find widespread use in the pharmaceutical industry. In addition, these nitrobenzenesulfonamides proved to be quite amenable to the solid-state synthesis of secondary amines for peptide synthesis and/or combinatorial chemistry [25].

Acknowledgment.

TF thanks his former and current coworkers, Drs. Xiaoqi Chen, Mui Cheung, Toshiyuki Kan, Tangqing Li, Ge Peng, Hidetoshi Tokuyama, Miss Yuko Hidai, Messrs. Satoshi Kobayashi, and Teppei Fujimoto for their tireless efforts devoted to these projects. Partial financial support from the Ministry of Education, Science, Sports and Culture is gratefully acknowledged.

REFERENCES AND NOTES

[1a] U. Pindur and R. Adam, *J. Heterocyclic Chem.*, **25**, 1 (1988); [b] J. E. Saxton, Indoles, Part Four, Wiley-Interscience, New York, 1983.

[2] T. Saegusa, S. Kobayashi, Y. Ito and N. Yasuda, *J. Am. Chem. Soc.*, **90**, 4182 (1968).

[3a] R. Leardini, G. F. Pedulli, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1320 (1984); [b] R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo and G. Zanardi, *J. Chem. Soc., Perkin. Trans. 1*, 1591 (1986); [c] R. Leardini, D. Nanni, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 757 (1989); [d] M. Bachi and D. Denenmark, *J. Am. Chem. Soc.*, **111**, 1886 (1989); [e] M. Bachi and D. Denenmark, *J. Org. Chem.*, **55**, 3442 (1990); [f] D. P. Curran and H. Liu, *J. Am. Chem. Soc.*, **113**, 2127 (1991).

[4] Methyl *o*-isocyanocinnamate **1a** was prepared from *o*-iodoaniline in a three-step sequence in 86% overall yield ((1) HCO_2H, Ac_2O, Py, CH_2Cl_2, 23°; (2) CH_2=$CHCO_2Me$, $Pd(OAc)_2$, $(o\text{-tolyl})_3P$, Et_3N, CH_3CN, 80°; (3) $COCl_2$, Et_3N, CH_2Cl_2, 0°). Other isonitriles **1b-f** were similarly prepared in 61 to 82% overall yields from *o*-iodoformanilide by palladium-mediated coupling reactions.

[5] A typical experimental procedure is as follows: A solution of an isonitrile (0.85 mmole), *n*-Bu_3SnH (0.93 mmole), and AIBN (0.04 mmole) in 5 ml of dry acetonitrile was heated at 100° for 1 hour in a tightly capped culture tube under an argon atmosphere. The reaction mixture was partitioned between 3 *N* HCl and ether. After washing the ethereal layer with a saturated KF solution, the desired indole was separated by flash silica gel chromatography.

[6a] P. Beak and W. K. Lee, *J. Org. Chem.*, **58**, 1109 (1993); [b] B. M. Trost and J. M. D. Fortunak, *Organometallics*, **1**, 7 (1982).

[7] The Stille coupling of 1-SEM-2-tributylstannylindole with a variety of halides has recently been reported: G. Palmisano and M. Santagostino, *Helv. Chim. Acta*, **76**, 2356 (1993).

[8a] F. K. Sheffy, J. P. Godschalx and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984); [b] J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, **109**, 813 (1987); [c] A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987).

[9] L. S. Liebeskind and R. W. Feng, *J. Org. Chem.*, **55**, 5359 (1990).

[10a] N. B. Perry, J. W. Blunt, J. D. McCombs and M. H. G. Munro, *J. Org. Chem.*, **51**, 5476 (1986); [b] N. B. Perry, J. W. Blunt, M. H. G. Munro, T. Higa and R. Sakai, *J. Org. Chem.*, **53**, 4127 (1988); [c] J. W. Blunt, V. L. Calder, G. D. Fenwick, R. J. Lake, J. D. McCombs, M. H. G. Munro and N. B. Perry, *J. Nat. Prod.*, **50**, 290 (1987).

[11] B. R. Copp, K. F. Fulton, N. B. Perry, J. W. Blunt and M. H. G. Munro, *J. Org. Chem.*, **59**, 8233 (1994).

[12] H. Kase, K. Iwahashi and Y. Matsuda, *J. Antibiot.*, **39**, 1059 (1986).

[13] J. L. Wood, B. M. Stoltz and H.-J. Dietrich, *J. Am. Chem. Soc.*, **117**, 10413 (1995).

[14] A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Letters*, **30**, 2581 (1989).

[15] A. Hazimierczuk, H. R. Cotlam, G. R. Revankar and R. K. Robins, *J. Am. Chem. Soc.*, **106**, 6379 (1984).

[16a] M. E. Kuehne and D. E. Podhorez, *J. Org. Chem.*, **50**, 924 (1985); [b] G. Kalaus, I. Greiner, M. Kajtar-Peredy, J. Brlik, L. Szabo and C. Szantay, *J. Org. Chem.*, **58**, 1434 (1993), and references cited therein.

[17] A. I. Scott, *Bioorg. Chem.*, **3**, 398 (1974) and references cited therein.

[18] T. Fukuyama, X. Chen and G. Peng, *J. Am. Chem. Soc.*, **116**, 3127 (1994).

[19a] O. Mitsunobu, *Synthesis*, 1 (1981); [b] D. L. Hughes, *Org. React.*, **42**, 335 (1992).

[20] J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris Jr. and S. M. Weinreb, *Tetrahedron Letters*, **30**, 5709 (1989).

[21] T. Tsunoda, J. Otsuka, Y. Yamamiya and S. Itô, *Chem. Letters*, 539 (1994).

[22] For general synthesis of amines, see: S. R. Sandler and W. Karo, Organic Functional Group Preparations, 2nd Ed, Academic, New York, 1983, Chapter 13.

[23] T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Letters*, **36**, 6373 (1995).

[24] T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai and T. Kan, *Tetrahedron Letters*, **38**, 5831 (1997).

[25a] P. Wipf and T. C. Henninger, *J. Org. Chem.*, **62**, 1586 (1997); [b] S. C. Miller and T. S. Scanlan, *J. Am. Chem. Soc.*, **119**, 2301 (1997).