Pergamon

Tetrahedron 56 (2000) 791–804

TETRAHEDRON

The Reactions of Nitrones with Indoles

Hélène Chalaye-Mauger, Jean-Noël Denis, Marie-Thérèse Averbuch-Pouchot and Yannick Vallée*

L.E.D.S.S., Laboratoire mixte CNRS, Université Joseph Fourier, B.P. 53, 38041 Grenoble, France

Received 10 September 1999; accepted 6 December 1999

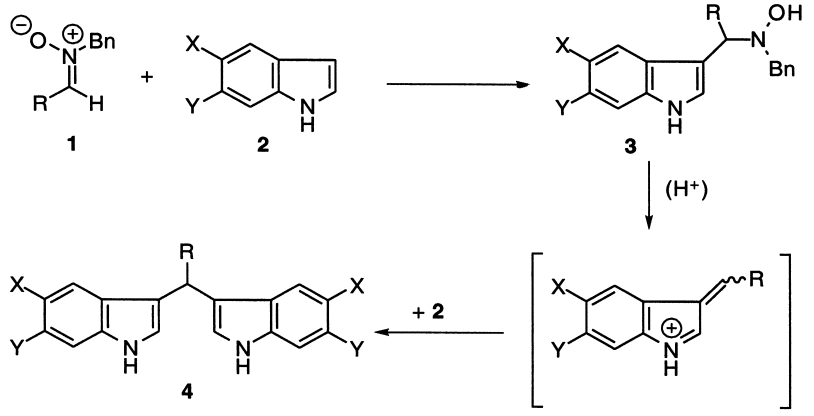
Abstract—The reaction of nitrones with various indole derivatives has been studied. When the reaction was promoted by $ClSiMe_3$, the isolated products were 3,3′-diindolylalkanes. With HCl as the activating reagent, 3-indolylhydroxylamines were isolated. The diastereoselectivity of this condensation with a nitrone derived from cysteine was investigated. A method for the introduction of an alkylhydroxylamino group onto position 2 of indole, the synthesis of three natural 3,3′-diindolylalkanes and of non-symmetric diindolylalkanes are also reported. © 2000 Elsevier Science Ltd. All rights reserved.

The chemistry of nitrones is a rapidly growing area. Even though the greatest part of the work is devoted to the study of their 1,3-dipolar cycloaddition reactions,[1] they are also involved in numerous reactions with nucleophiles. Not only organometallics,[2,3] but also electron-rich aromatic compounds can be made to react with nitrones. In a preliminary communication,[4] we have reported that indole derivatives react with nitrones (Scheme 1). The obtained products are of two types: (i) the hydroxylamines **3** resulting from the condensation of one molecule of nitrone with one indole nucleus, and (ii) bis-indole derivatives of type **4** formed by the reaction of an intermediate 3-alkylidene-3*H*-indolium cation with the starting indole.

In this paper, we detail our findings about these reactions. In particular, the role of the activation agent is studied and the first diastereoselective examples of these condensations are presented. A method for introducing an alkylhydroxylamino group on position 2 of indole is also described.

Activation of Nitrones

No reaction occurred when a nitrone and indole were mixed in toluene, methanol or dichloromethane. This means that, if any reaction is wanted, the nitrone has to be activated. The goal of such activation should be to render the nitrone more electrophilic, i.e. to make the carbon atom of the nitrone function more positive. This can be obtained by introducing a proton or a silyl group[5] on its oxygen atom. Four test experiments were run with the benzyl nitrone of propanal **1a** (Scheme 2). This nitrone was dissolved in $CDCl_3$ and

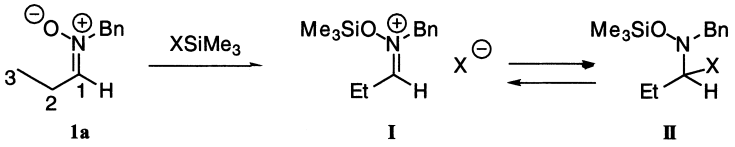


Scheme 1.

Keywords: indoles; nitrones; hydroxylamines; natural products.

* Corresponding author. Tel.: +33-4-76-63-57-96; fax: +33-4-76-51-43-82; e-mail: yannick.vallee@ujf-grenoble.fr

PII: S0040-4020(99)01051-0



Scheme 2.

Table 1. NMR data (δ ppm) for nitrone **1a**, and nitrone **1a** mixed with various activating agents

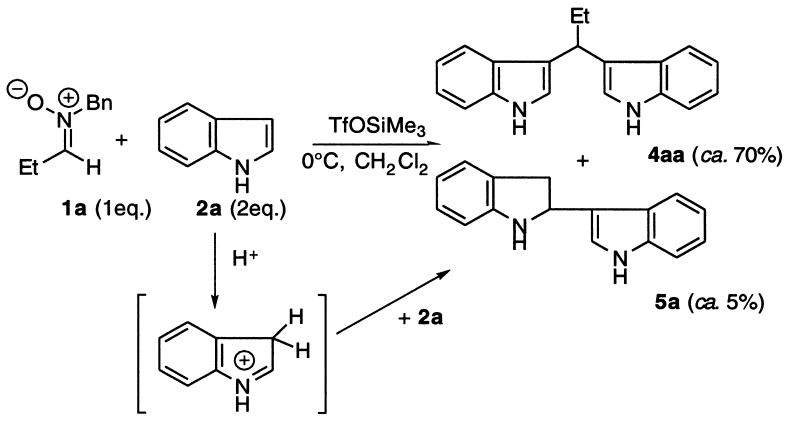
Activating agent	None	$TfOSiMe_3$	$ClSiMe_3$	$ClSiEt_3$	33% HCl/H_2O
^1H NMR					
H-1	6.61	8.76	7.07	6.81	7.91
H-2	2.50	2.84	2.47	2.51	2.63
H-3	1.08	1.40	1.04	1.08	1.14
CH_2Ph	4.88	5.42	4.95	4.93	5.27
^{13}C NMR					
C-1	140.6	170.9	144.4		

mixed in NMR tubes with 1 equiv. of different sources of silicon ($TfOSiMe_3$, $ClSiMe_3$ and $ClSiEt_3$) and with 33% aqueous HCl. The obtained ^1H and ^{13}C NMR data are listed in Table 1. In each case, the resonance of the 'aldehydic' proton is shifted towards low fields as compared to the free nitrone. This demonstrates the formation of new species. Clearly, the more iminium-like product is the triflate salt (H-1: 8.76 ppm). In the case of a chloride counterion, one must be in presence of a more tightly bonded pair and the observed species might be described as a mixture of the two limit forms **I** and **II** (Scheme 2). The triflate anion being much less nucleophilic than Cl^-, the bonded sp^3 form **II** is probably much less important when $X^-=TfO^-$. Examination of ^{13}C NMR data confirms this proposal: in the case of the triflate, the C=N carbon is observed in the iminium carbon region; with the chloride anion, the observed shift is intermediate between the shifts of an iminium (ca. 170 ppm) and of an α-chloramine (80–90 ppm).[6] Thus, $TfOSiMe_3$ is expected to be a stronger activation agent than $ClSiMe_3$. It should be noticed that $ClSiEt_3$ seems to be the worst tested reagent. This is probably due to the electron-donating properties of its three ethyl groups. Finally, a proton should be an acceptable reagent. Care must be taken, however, due to the fact that the acidic water solution rapidly hydrolyses the nitrone to give the corresponding aldehyde, propanal.

Condensations using Trimethylsilyl Triflate

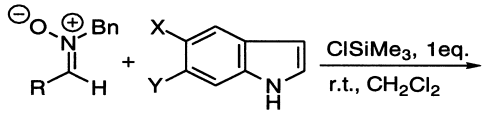
A first experiment was run using the benzylnitrone of propanal **1a** and indole **2a** in the presence of $TfOSiMe_3$ (1:1 ratio) in anhydrous CH_2Cl_2 at room temperature. After 2 h, a complex mixture resulted in which we were able to identify 1,1-bis(3′-indolyl)propane **4aa** as the major product and some remaining starting nitrone. As the formation of the diindolylalkane requires 2 mol of indole per mole of nitrone, the reaction was repeated using a nitrone to indole ratio of 1–2. The reaction was run at 0°C to minimize the formation of side products. It was rapid and relatively clean giving **4aa** in high yield. However, **4aa** was accompanied by some indole dimer **5a**[7] (ca. 5%, Scheme 3). The formation of **5a** can be explained by protonation of indole by the formed triflic acid. The obtained cation is then attacked by another indole molecule to give the dimer **5a**. Even though **5a** was a very minor by-product, we were unable to separate it from **4aa** by liquid chromatography, and were unable to obtain pure **4aa** in this way.

Thus, the formation of triflic acid during the condensation of a nitrone onto indole is a severe drawback to the use of $TfOSiMe_3$ as the activation reagent. HCl being less acidic than TfOH, we thought that such drawback could be absent for $ClSiMe_3$.

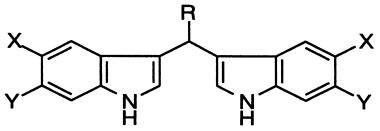


Scheme 3.

Table 2. Yields of the reaction of nitrones with indoles in the presence of $ClSiMe_3$



1a-g (1eq.) **2a-d** (2eq.)



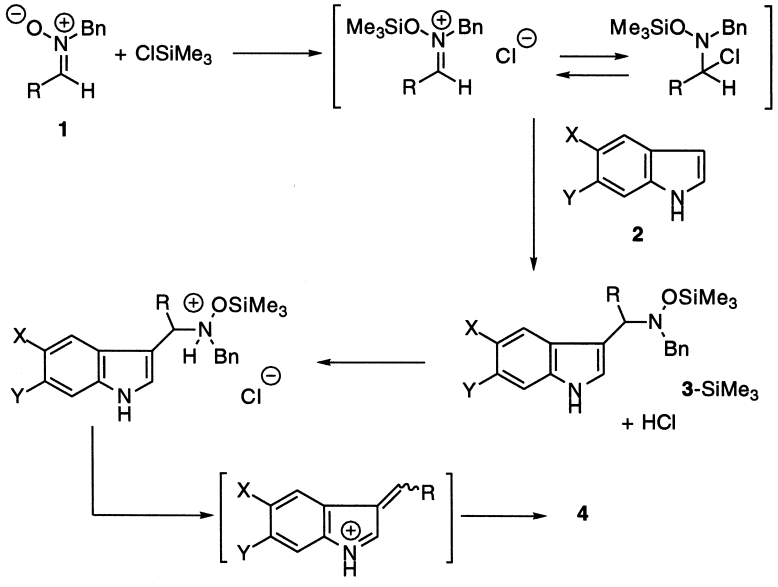
4

Entry	Nitrone	R	Indole	X, Y	Reaction time (h)	Bis-indole	Yield (%)
1	**1a**	Et	**2a**	H, H	2	**4aa**	85
2	**1b**	Me			17	**4ba**	83
3	**1c**	Pr^i			14	**4ca**	97
4	**1d**	CH_2OBn			15.5	**4da**	91
5	**1e**	CH_2NHBoc			8.5	**4ea**	56
6	**1f**	Ph			48	**4fa**	88
7	**1g**	*p*-NO_2–C_6H_4			72	**4ga**	75
8	**1a**	Et	**2b**	MeO, H	8.5	**4ab**	86
9	**1a**	Et	**2c**	Br, H	72	**4ac**	88
10	**1c**	Pr^i			64	**4cc**	60
11	**1e**	CH_2NHBoc			48	**4ec**	46
12	**1e**	CH_2NHBoc	**2d**	H, Br	54	**4ed**	31

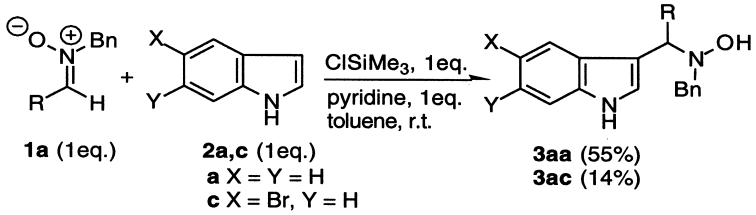
Condensations using Trimethylsilyl Chloride

A series of condensations was run with various indole derivatives **2a–d** (2 equiv.) and nitrones **1a–g** (1 equiv.) using 1 equiv. $ClSiMe_3$ as the activator (Table 2). They were monitored by TLC and found to be relatively slow at room temperature. Yields however were generally good except in the case of the α-amino nitrone **1e**. This nitrone was found to be poorly stable under the reaction conditions, probably because of the possible cleavage of the *N*-Boc protective group by the formed HCl. Not only indole **2a** but also an electron-rich indole such as **2b**, and the electron-poor derivatives **2c,d** can take part in this reaction, without noticeable change in the yield (compare entries 1, 8 and 9). Aromatic nitrones also give the bis-indole derivatives. It should be noticed that the other possible products of these reactions, compounds **3** (Scheme 1), were never detected.

It is probable that the first formed intermediate is the *O*-silylated derivative of **3** (Scheme 4). Formation of the 3-alkylidene-3*H*-indolium ion, which must be formed en route to compound **4**, thus requires the protonation of **3**-$SiMe_3$. This protonation is possible because of the liberation of HCl during the first condensation step. We reasoned that trapping of HCl by a base could eliminate the protonation of **3**-$SiMe_3$, and would allow the isolation of mono-adduct **3**.



Scheme 4.



Scheme 5.

The best results were obtained with pyridine as the base in anhydrous toluene at room temperature. Under these conditions (Scheme 5), the condensation of nitrone **1a** with indole gave the hydroxylamine **3aa** as the major isolated product. However, the yield was only moderate. Furthermore, when the same conditions were applied to 5-bromoindole, the isolated yield was only 14%. Clearly, better conditions were to be looked for if the goal was to obtain reasonable yields of indolic hydroxylamines **3**.

Condensations using HCl

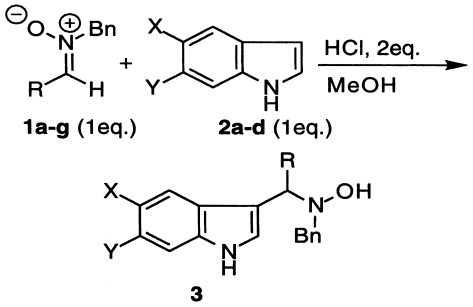
When equimolar amounts of indole and nitrone **1a** were mixed at room temperature in CH_2Cl_2 in the presence of 1 equiv. of aqueous HCl, a mixture of the starting nitrone and the bis-indole derivative **4aa** (ratio 44:56) was obtained. The formation of a small amount of the indole dimer **5a** was also noticed. When the same reaction was conducted at 0°C, the major product was the hydroxylamine **3aa** still accompanied by some bis-indole and starting compounds. As the formation of **4aa** may be due in some part to the transient formation of propanal in the reaction mixture by hydrolysis of the nitrone (vide supra), we decided to use anhydrous HCl. It was generated by addition of acetyl chloride into anhydrous methanol. The best results were obtained using 2 equiv. of AcCl (and thus 2 equiv. of HCl) for 1 equiv. of indole and 1 equiv. of nitrone (Table 3). Alternatively, trifluoroacetic acid in methanol or pyridinium *p*-toluenesulfonate (PPTS) in toluene could also be used. The yields however are lower and with PPTS the presence of some **4aa** was noticed.

Yields using HCl in methanol were generally good. Exceptions were condensations using the nitrones derived from isobutyraldehyde and benzaldehyde (entries 3 and 6), in which the formation of the 3*H*-indolium cation is favored by the good electron-donating properties of the substituents and, for the phenyl group, by the possible delocalization of the positive charge. In these cases it was not possible to stop the reaction at the hydroxylamine stage and the bis-indoles were the only products. Interestingly, when an electron-withdrawing group was introduced on the phenyl group (NO_2, entry 7), isolation of the hydroxylamine was again possible.

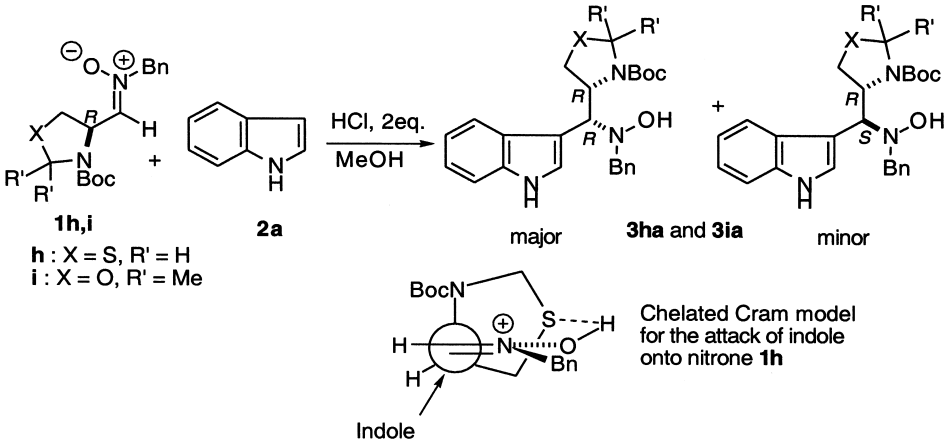
Diastereoselective Condensations

The condensation of a nitrone with an indole to give a hydroxylamine creates a new stereogenic center. Such chiral

Table 3. Yields of the reaction of nitrones with indoles in the presence of HCl



Entry	Nitrone	R	Indole	X, Y	Temperature (°C)	Reaction time (h)	Hydroxylamine	Yield (%)
1	**1a**	Et	**2a**	H, H	0	2	**3aa**	94
2	**1b**	Me			0	2	**3ba**	87
3	**1c**	Pr^i			0	2	**3ca**	0
4	**1d**	CH_2OBn			0	1	**3da**	88
5	**1e**	CH_2NHBoc			0	1	**3ea**	95
6	**1f**	Ph			0	1	**3fa**	0
7	**1g**	*p*-$NO_2C_6H_4$			0	0.5	**3ga**	44
8	**1a**	Et	**2b**	MeO, H	−10	1	**3ab**	83
9	**1b**	Me			−10	1	**3bb**	88
10	**1d**	CH_2OBn			−10	1	**3db**	93
11	**1e**	CH_2NHBoc			−10	1	**3eb**	95
12	**1a**	Et	**2c**	Br, H	r.t.	3	**3ac**	70
13	**1b**	Me			r.t.	3	**3bc**	82
14	**1e**	CH_2NHBoc			0	4	**3ec**	83
15	**1e**	CH_2NHBoc	**2d**	H, Br	0	4	**3ed**	78



Scheme 6.

centers are present for instance in some newly described azaelliptitoxine analogues.[8] With the goal of performing the synthesis of such compounds we needed to determine if these condensations could be diastereoselective.

Two α-chiral nitrones **1h,i** were prepared respectively from L-cysteine and L-serine (Scheme 6). The best result was obtained from the sulfurated nitrone **1h**. Treatment of **1h** and indole by dry HCl (2 equiv.) in methanol for 4 h at 0°C leads to the expected hydroxylamine **3ha** in 68% yield (traces of the corresponding bis-indole and of indole dimer **5a** were also detected by TLC). As expected, **3ha** was obtained as a mixture of stereoisomers. These stereoisomers were separated by liquid chromatography and the diastereoisomeric ratio was found to be 92:8. The (*R*,*R*)-configuration of the major isomer was determined by X-ray crystallography of a single crystal obtained by recrystallization from ethanol (Fig. 1). This configuration can be rationalized using a cyclic Cram model (Scheme 6) in which the activating proton is chelated between the nitrone oxygen atom and the sulfur atom of the thiazolidine ring.

The result with the serine derived nitrone was less clear. The crude product contained the hydroxylamine **3ia** as the major component. However, it was contaminated by some indole dimer **5a** and we were unable to isolate it in pure form. From what can be observed in the ^{1}H NMR spectrum of impure **3ia**, it seems that one diastereomer, to which we attribute the (*R*,*R*)-configuration by analogy with the previous example, largely dominates. However, it was not pure enough to ensure that only one isomer was present.

Condensations on Position 2 of Indole

Position 3 of indole is the most reactive position for Friedel–Crafts type reactions such as the condensation of nitrones described supra. However, it could be interesting to introduce an alkylhydroxylamino group on other positions of indole. For instance, some eudistomins,[9] which are powerful antiviral molecules, possess a C–N–O sub-unit attached on an indole nucleus at position 2. In order to create such a framework, we have tested an ortho-lithiation process.

Among the various possible ortho-lithiation procedures, we chose a method developed by Katritzky et al.[10] The major advantage of this method is that the orienting group is both easily introduced and removed in situ just before and after the condensation step (Scheme 7). Thus, indole **2a** was

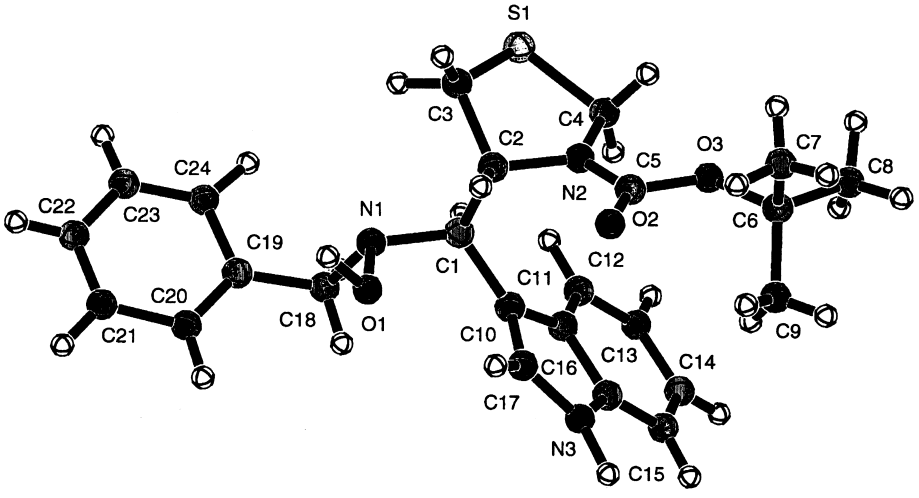
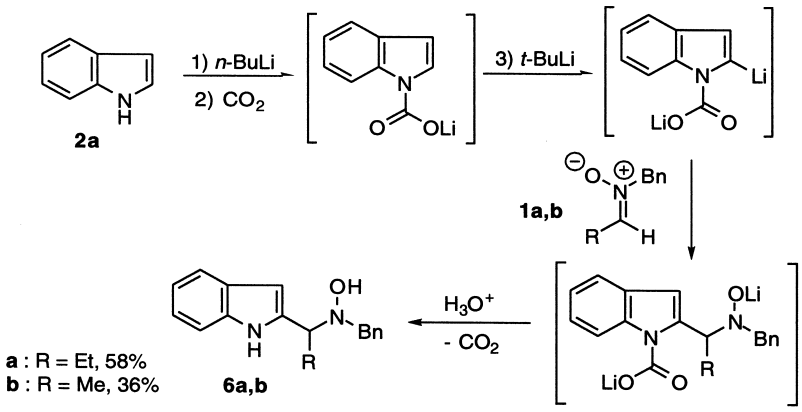


Figure 1.



Scheme 7.

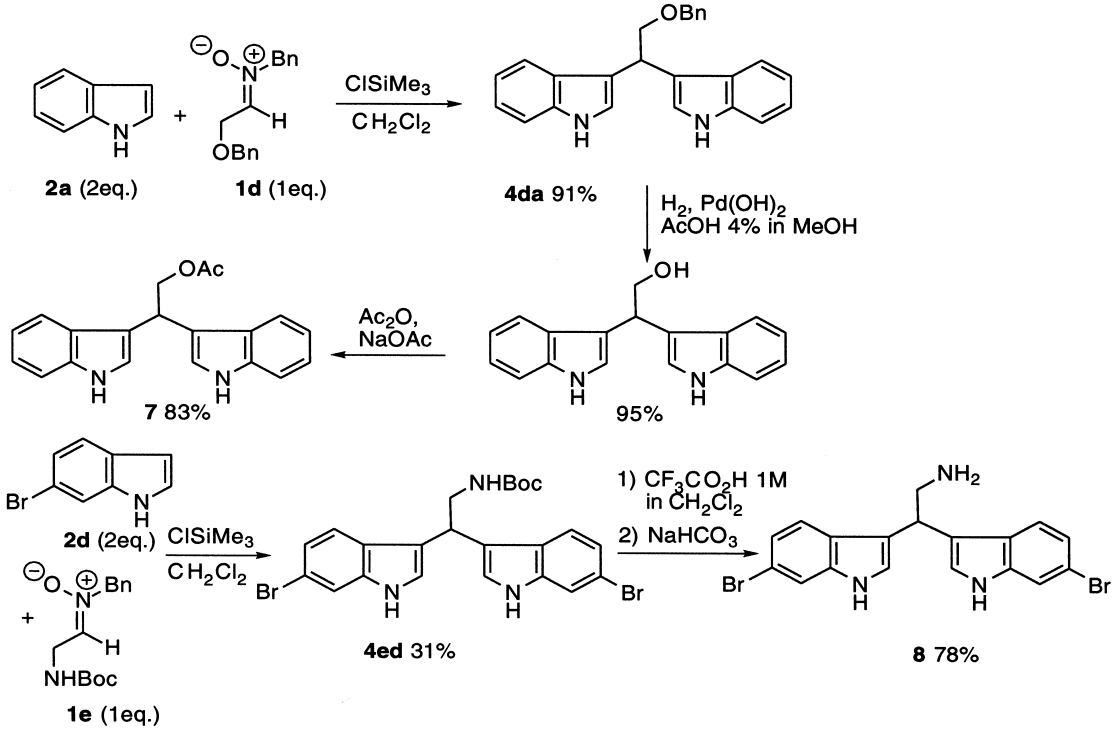
deprotonated by *n*-BuLi and the formed anion was treated by solid CO_2. Subsequent treatment of the obtained carboxylate by *t*-BuLi gave a dianion which reacted with nitrones **1a,b**. Even though the yields were only moderate, the possibility of obtaining condensations on position 2 was demonstrated. The hydroxylamines **6a,b** were isolated in 58 and 36% yields.

Synthesis of Naturally Occurring 3,3′-Diindolylalkanes

The usual way to obtain 3,3′-diindolylalkanes consists of treating an indole derivative with an aldehyde in an acidic medium.[11–13] However, yields are often only moderate. In particular, because of the relatively strong acid conditions needed, the indole dimer **5a** (or one of its homologues) can be expected to be a usual by-product.[7,11] Furthermore, acid-sensitive aldehydes cannot be used. We report thereafter the synthesis of three simple natural diindolylalkanes[4] with the goal of showing that the detour through nitrones, rather than the direct condensation of aldehydes, is of reasonable synthetic interest.

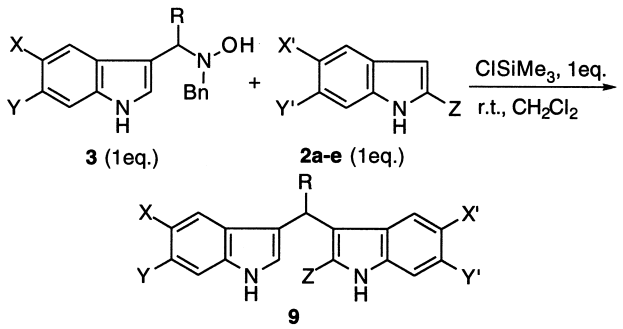
1,1-Bis(3′-indolyl)ethane **4ba** (Table 2) is a metabolite of the bacteria *Vibrio parahaemolyticus* isolated from the toxic mucus of the Australian box-fish *Ostracion cubicus*.[14] This molecule has been named vibrindole A and biological tests demonstrated its activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Staphylococcus albus*. It has already been synthesized from acetaldehyde and indole in acetic acid and the reported yield was 58%[12] (to be compared with 83% in our case).

Streptindole **7** (Scheme 8) is the adduct of two molecules of indole with one molecule of acetoxyacetaldehyde.[15,16] It has been isolated from intestinal bacteria *Streptococcus faecium* IB37 and causes DNA lesions in *Bacillus subtilis* cells. It



Scheme 8.

Table 4. Yields of bis-indoles from hydroxylamines **3** and indoles **2**



Entry	Hydroxylamine	R, X, Y	Indole	X′, Y′, Z	Reaction time (h)	Bis-indole	Yield (%)
1	**3aa**	Et, H, H	**2c**	Br, H, H	24	**9aac**	76
2	**3aa**		**2d**	H, Br, H	18	**9aad**	84
3	**3aa**		**2b**	MeO, H, H	14	**9aab**	83
4	**3aa**		**2e**	H, H, Me	14	**9aae**	74
5	**3ba**	Me, H, H	**2c**	Br, H, H	24	**9bac**	51
6	**3bc**	Me, Br, H	**2a**	H, H, H	18	**9bac**	53
7	**3ba**	Me, H, H	**2b**	MeO, H, H	14	**9bab**	63
8	**3bb**	Me, MeO, H	**2a**	H, H, H	18	**9bab**	57
9	**3da**	CH_2OBn, H, H	**2c**	Br, H, H	24	**9dac**	83
10	**3da**		**2b**	MeO, H, H	14	**9dab**	76
11	**3ea**	CH_2NHBoc, H, H	**2d**	H, Br, H	20	**9ead**	48

was first synthesized in 2% yield by reaction of acetoxyacetaldehyde with indole.[16] Using glyoxylic acid as starting material, Hogan and Sainsbury[17] obtained **7** in four steps and with a 42% overall yield from indole. Our synthesis (Scheme 8) started with indole and nitrone **1d**. The overall yield of this three step strategy was 72% from indole. As nitrone **1d** was obtained in 95% yield from benzyloxyacetaldehyde, the overall yield from this aldehyde was 68%.

2,2-Bis(6′-bromo-3′-indolyl)ethylamine **8** was isolated in 1991 from the tunicate *Didemnum candidum*.[18] It is also present in *Orina* sp. sponges.[19] We have synthesized this compound for the first time[4] in two steps from 6-bromoindole **2d** and nitrone **1e** (Scheme 8). The overall yield, however, was only 24%, due to the low yield of the first step (31%).

Synthesis of Non-Symmetric 3,3′-Diindolylalkanes

In Scheme 4 we have presented a mechanism which explains the formation of bis-indole derivatives from indoles and nitrones in the presence of $ClSiMe_3$. We proposed that an alkylidene-3*H*-indolium cation was formed and reacted with another indole molecule. If this is true, treatment of an isolated hydroxylamine **3** by $ClSiMe_3$ should give the same alkylidene-3*H*-indolium cation, which would be able to react with any added nucleophile. We decided to test this possibility,[4] using as the new nucleophile an indole derivative different from the one which was used to synthesize the hydroxylamine. The expected products are then non-symmetric diindolylalkanes. Our results are summarized in Table 4.

To the best of our knowledge, this is the first reported general synthesis of non-symmetric diindolylalkanes.[4] Yields are moderate to good. Examination of entries 5–8 shows that the substituents can be introduced in the final products **9** (**9bac** for entries 5 and 6 and **9bab** for entries 7 and 8) either from the hydroxylamine **3** or from the added indole **2** without major change in the yields.

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride and methanol from magnesium. Acetyl chloride, trimethylsilyl chloride and trifluoroacetic acid were distilled before use. All other commercially available reactants and solvents were used without purification. Thin-layer chromatography was performed on Merck $60F_{254}$ (0.2 mm) sheets. Merck Kieselgel SI 60 silica gel (0.063–0.200 mm) was employed for column chromatography. Brucker AC 200, AM 300, WM 250 and Avance 300 spectrometers were used to record the ^1H and ^{13}C NMR spectra. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hertz. Mass spectra were obtained on a Nermag R10 mass spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Melting points were obtained with a Büchi–Tottoli apparatus and are not corrected. Microanalysis were performed by the 'Service Central d'Analyse du CNRS' at Vernaison (France).

Synthesis of nitrones

Nitrones were prepared according to the procedure described by Dondoni and coworkers.[20] Most of them were previously known.[3a,5,20–23]

(*Z*)-*N*-[2-(Benzyloxy)ethylidene]benzylamine *N*-oxide (1d). Yield: 95%. Mp: 95.5–96.5°C. ^1H NMR ($CDCl_3$, 200 MHz): 2.92 (dd, J=1.4, 4.4 Hz, 2H, OCH_2); 4.52 (s, 2H, OCH_2Ph); 4.85 (s, 2H, NCH_2Ph); 6.78 (t, J=4.4 Hz,

^{1}H, HC=N); 7.21–7.44 (m, 10H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 66.0 (CH_2); 68.8 (CH_2); 73.6 (CH_2); 127.8 (CH); 128.3 (CH); 128.9 (CH); 129.0 (CH); 129.4 (CH); 132.0 (C); 137.0 (C=N). SM (CI, NH_3+isobutane): *m*/*z* 256 (MH^+). Anal. calcd for $C_{16}H_{17}NO_2$: C: 75.27%, H: 6.71%, N: 5.49%; found: C: 75.23%, H: 6.69%, N: 5.46%.

(*Z*)-*N*-[2-(*tert*-Butoxycarbonylamino)ethylidene]benzylamine *N*-oxide (1e). Yield: 88%. Mp: 91–92°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.42 (s, 9H, $C(CH_3)_3$); 4.02 (t, *J*=5.0 Hz, 2H, CH_2); 4.86 (s, 2H, CH_2Ph); 5.49 (broad s, ^{1}H, NHBoc); 6.86 (broad s, ^{1}H, HC=N); 7.34–7.52 (m, 5H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.2 ($C(CH_3)_3$); 37.0 (CH_2); 69.1 (CH_2); 79.7 ($C(CH_3)_3$); 128.9 (CH); 129.0 (CH); 129.2 (CH); 132.4 (C); 135.8 (C=N); 156.0 (CO_2). SM (CI, NH_3+isobutane): *m*/*z* 265 (MH^+). Anal. calcd for $C_{14}H_{20}N_2O_3$: C: 63.64%, H: 7.57%, N: 10.60%; found: C: 63.63%, H: 7.47%, N: 10.49%.

(*Z*)-*N*-(4-Nitrobenzylidene)benzylamine *N*-oxide (1g). Yield 73%. Mp: 117–118°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.11 (s, 2H, CH_2Ph); 7.42–7.51 (m, 6H, C_6H_5, HC=N); 8.23 (d, *J*=9.0 Hz, 2H, CH_{arom}); 8.35 (d, *J*=9.5 Hz, 2H, CH_{arom}). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 72.1 (CH_2); 123.7 (CH); 128.8 (CH); 129.1 (CH); 129.4 (CH); 132.1 (C=N); 132.5 (C); 135.9 (C); 147.8 (C). MS (CDI, NH_3+isobutane): *m*/*z* 257 (MH^+). Anal. calcd for $C_{14}H_{12}N_2O_3$: C: 65.62%, H: 4.69%, N: 10.94%; found: C: 65.87%, H: 4.64%, N: 10.96%.

Synthesis of diindolylalkanes

A mixture of the nitrone (1 mmol) and Me_3SiCl (1 mmol) in 10 mL of anhydrous CH_2Cl_2 was stirred for 5 min at r.t. The indole derivative (2 mmol) was then added and the reaction was monitored by TLC (silica gel, diethyl ether/pentane; 1:1). After completion of the reaction, the mixture was treated by an aqueous solution of $NaHCO_3$. The organic layer was washed twice with water, once with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum and the obtained residue was purified by column chromatography over silica gel.

Compounds **4aa**,[24] **4ba**,[12,24] **4fa**[12] and **4ga**[12] were previously known.

1,1-Di(3′-indolyl)-2-methylpropane (4ca). Yield: 97%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.99 (d, *J*=6.5 Hz, 6H, 2×CH_3); 2.55–2.70 (m, ^{1}H, CH); 4.23 (d, *J*=8.0 Hz, ^{1}H, CH); 6.97 (d, *J*=2.0 Hz, 2H, CH_{arom}); 7.00–7.13 (m, 4H, CH_{arom}); 7.22 (d, *J*=8.0 Hz, 2H, CH_{arom}); 7.62 (d, *J*=8.0 Hz, 2H, CH_{arom}); 7.71 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 21.8 (2×CH_3); 32.8 (CH); 41.0 (CH); 111.0 (CH); 118.9 (CH); 119.6 (CH); 121.5 (CH); 121.6 (CH); 127.6 (C); 136.2 (C). MS (CI, NH_3+isobutane): *m*/*z* 288 (M^+). Anal. calcd for $C_{20}H_{20}N_2$: C: 83.31%, H: 6.99%, N: 9.71%; found: C: 83.40%, H: 6.99%, N: 9.47%.

1-Benzyloxy-2,2-di(3′-indolyl)ethane (4da). Yield: 91%. Mp: 59–60°C. ^{1}H NMR ($CDCl_3$, 250 MHz): 4.04 (d, *J*=7.1 Hz, 2H, CH_2); 4.51 (s, 2H, CH_2Ph); 4.82 (t, *J*=7.1 Hz, ^{1}H, CH); 6.63 (d, *J*=2.4 Hz, 2H, CH_{arom}); 6.94–7.22 (m, 1^{1}H, CH_{arom}); 7.47 (d, *J*=7.9 Hz, 2H, CH_{arom}); 7.59 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 34.4 (CH); 72.8 (CH_2); 73.3 (CH_2); 111.1 (CH); 116.6 (C); 118.9 (CH); 119.3 (CH); 121.6 (CH); 122.5 (CH); 126.8 (C); 127.5 (CH); 127.7 (CH); 128.2 (CH); 136.2 (C); 138.2 (C). MS (CI, NH_3+isobutane): *m*/*z* 366 (M^+). Anal. calcd for $C_{25}H_{22}N_2O$: C: 81.94%, H: 6.05%, N: 7.64%; found C: 81.75%, H: 6.24%, N: 7.43%.

***N*-(*tert*-Butoxycarbonyl)-2,2-di(3′-indolyl)ethylamine (4ea).** Yield: 56%. Mp: 203–203.5°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.42 (s, 9H, $C(CH_3)_3$); 3.92 (t, *J*=6.6 Hz, 2H, CH_2); 4.57–4.74 (m, ^{1}H, NH); 4.71 (nearly t, *J*=7.2, 7.5 Hz, ^{1}H, CH); 6.98 (d, *J*=2.0 Hz, 2H, CH_{arom}); 7.01–7.21 (m, 4H, CH_{arom}); 7.35 (d, *J*=8.2 Hz, 2H, CH_{arom}); 7.61 (d, *J*=7.9 Hz, 2H, CH_{arom}); 8.02 (broad s, 2H, NH). ^{13}C NMR (DMSO, 100.6 MHz): 28.3 ($C(CH_3)_3$); 33.8 (CH); 45.0 (CH_2); 77.5 ($C(CH_3)_3$); 111.3 (CH); 116.4 (C); 118.0 (CH); 118.9 (CH); 120.7 (CH); 122.3 (CH); 126.9 (C); 136.4 (C); 155.7 (CO_2). MS (CI, NH_3+isobutane): *m*/*z* 375 (MH^+). Anal. calcd for $C_{23}H_{25}N_3O_2$: C: 73.57%, H: 6.71%, N: 11.19%; found: C: 73.29%, H: 6.66%, N: 11.22%.

1,1-Di(5′-methoxy-3′-indolyl)propane (4ab). Yield: 86%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.01 (t, *J*=7.2 Hz, 3H, CH_3); 2.15–2.30 (m, 2H, CH_2); 3.76 (s, 6H, 2×OCH_3); 4.26 (t, *J*=7.5 Hz, ^{1}H, CH); 6.80 (dd, *J*=2.0, 8.6 Hz, 2H, CH_{arom}); 6.96 (d, *J*=2.0 Hz, 2H, CH_{arom}); 7.03 (d, *J*=2.0 Hz, 2H, CH_{arom}); 7.20 (d, *J*=8.6 Hz, 2H, CH_{arom}); 7.77 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 13.0 (CH_3); 28.4 (CH_2); 35.9 (OCH_3); 55.9 (CH); 101.9 (CH); 111.5 (CH); 111.6 (CH); 119.8 (C); 122.3 (CH); 127.6 (C); 131.8 (C); 153.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 335 (MH^+). Anal. calcd for $C_2{}^1H_{22}N_2O_2$: C: 75.42%, H: 6.63%, N: 8.38%; C: 75.51%, H: 6.77%, N: 8.07%.

1,1-Di(5′-bromo-3′-indolyl)propane (4ac). Yield: 88%. Mp: 60–64°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.95 (t, *J*=7.4 Hz, 3H, CH_3); 2.17 (quint., *J*=7.4 Hz, 2H, CH_2); 4.19 (t, *J*=7.4 Hz, ^{1}H, CH); 6.95 (d, *J*=2.2 Hz, 2H, CH_{arom}); 7.01–7.29 (m, 4H, CH_{arom}); 7.64 (d, *J*=1.6 Hz, 2H, CH_{arom}); 7.86 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 12.8 (CH_3); 28.1 (CH_2); 35.7 (CH); 112.2 (C); 112.6 (CH); 119.1 (C); 121.9 (CH); 122.7 (CH); 124.5 (CH); 128.5 (C); 135.1 (C). MS (CI, NH_3+isobutane): *m*/*z* 448, 450 and 452 (MH^++NH_3). Anal. calcd for $C_{19}H_{16}Br_2N_2$: C: 52.81%, H: 3.73%, N: 6.48%; found: C: 52.62%, H: 3.78%, N: 6.21%.

1,1-Di(5′-bromo-3′-indolyl)-2-methylpropane (4cc). Yield: 60%. Mp: 150–152°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.99 (d, *J*=6.8 Hz, 6H, 2×CH_3); 2.50–2.70 (m, ^{1}H, C*H*(CH_3)$_2$); 4.07 (d, *J*=8.4 Hz, ^{1}H, CH); 7.12–7.41 (m, 6H, CH_{arom}); 7.19 (s, 2H, CH_{arom}); 7.97 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 21.8 (2×CH_3); 32.5 (CH); 41.4 (CH); 112.5 (CH); 119.0 (C); 122.2 (CH); 124.9 (CH); 129.2 (C); 135.0 (C). MS (CI, NH_3+isobutane): *m*/*z* 462, 464 and 466 (MH^++NH_3), 445, 447 and 449 (MH^+). Anal. calcd for $C_{20}H_{18}Br_2N_2$: C: 53.84%, H: 4.07%, N: 6.28%; found C: 54.24%, H: 4.09%, N: 6.26%.

***N*-(*tert*-Butoxycarbonyl)-2,2-di(5′-bromo-3′-indolyl)-ethylamine (4ec).** Yield: 46%. Mp: 203–203.5°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.43 (s, 9H, $C(CH_3)_3$); 3.86 (nearly t, J=6.4 Hz, 2H, CH_2N); 4.57 (nearly t, J=6.4 Hz, 2H, CHN, NH); 7.05 (broad s, 2H, CH_{arom}); 7.24 (broad s, 4H, CH_{arom}); 7.64 (broad s, 2H, CH_{arom}); 8.12 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.4 ($C(CH_3)_3$); 34.6 (CH); 44.9 (CH_2); 79.5 ($C(CH_3)_3$); 112.7 (CH); 116.4 (C); 122.0 (CH); 123.2 (CH); 125.1 (CH); 128.5 (C); 135.3 (C); 156.0 (CO_2). MS (CI, NH_3+isobutane): m/z 531, 533 and 535 (M^+).

***N*-(*tert*-Butoxycarbonyl)-2,2-di(6′-bromo-3′-indolyl)-ethylamine (4ed).** Yield: 31%. Mp: 240–242°C. ^{1}H NMR (DMSO, 200 MHz): 1.32 (s, 9H, $C(CH_3)_3$); 3.58 (t, J=6.2 Hz, 2H, CH_2); 4.60 (t, J=6.2 Hz, ^{1}H, CH); 6.82 (t, J=6.2 Hz, ^{1}H, NH); 6.97–7.48 (m, 8H, CH_{arom}); 10.96 (broad s, 2H, NH). ^{13}C NMR (DMSO, 100.6 MHz): 28.2 ($C(CH_3)_3$); 33.5 (CH); 44.9 (CH_2); 77.5 ($C(CH_3)_3$); 113.6 (C); 113.9 (CH); 116.4 (C); 120.5 (CH); 120.9 (CH); 123.5 (CH); 125.9 (C); 137.3 (C); 155.7 (CO_2). MS (CI, NH_3+isobutane): m/z 531, 533 and 535 (M^+). Anal. calcd for $C_{23}H_{23}Br_2N_3O_2$: C: 51.80%, H: 4.35%, N: 7.88%; found: C: 52.05%, H: 4.64%, N: 7.67%.

Synthesis of 3-indolylhydroxylamines

A cold solution (0°C) of dry HCl in methanol was prepared by addition of acetyl chloride (2 mmol) to methanol. The nitrone and the indole (1 mmol each) were added to this solution. The reaction was monitored by TLC (silica gel, diethyl ether/pentane; 1:1) until completion. A saturated aqueous solution of $NaHCO_3$ was then added. The mixture was extracted three times with CH_2Cl_2, and the collected organic phases washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent under vacuum, the crude product was purified either by several washings with pentane, by crystallization from a CH_2Cl_2/pentane mixture or by column chromatography on silica gel.

***N*-Benzyl-*N*-hydroxy-1-(3′-indolyl)propylamine (3aa).** Yield: 94%. Mp: 142–143°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.86 (t, J=7.4 Hz, 3H, CH_3); 1.84–2.06 (m, ^{1}H, ^{1}H of CH_2); 2.14–2.34 (m, ^{1}H, ^{1}H of CH_2); 3.71 (ABq, J_{AB}=13.5 Hz, $\delta_A-\delta_B$=36.3, 2H, CH_2Ph); 3.97 (dd, J=5.1, 9.1 Hz, ^{1}H, CHN); 4.78 (broad s, ^{1}H, NOH); 7.01–7.80 (m, 10H, CH_{arom}); 8.12 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 11.4 (CH_3); 26.3 (CH_2); 61.8 (CH_2); 66.2 (CHN); 111.1 (CH); 114.6 (C); 119.5 (CH); 120.2 (CH); 122.1 (CH); 123.2 (CH); 126.9 (CH); 127.4 (C); 128.1 (CH); 129.2 (CH); 136.3 (C); 138.8 (C). MS (CI, NH_3+isobutane): m/z 281 (MH^+). Anal. calcd for $C_{18}H_{20}N_2O$: C: 77.11%, H: 7.19%, N: 9.99%; found C: 76.66%, H: 7.17%, N: 9.88%.

***N*-Benzyl-*N*-hydroxy-1-(3′-indolyl)ethylamine (3ba).** Yield: 87%. Mp: 97–99°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.61 (d, J=6.9 Hz, 3H, CH_3); 3.74 (ABq, J_{AB}=13.4 Hz, $\delta_A-\delta_B$=26.7, 2H, CH_2Ph); 4.27 (q, J=6.9 Hz, ^{1}H, CHN); 5.05 (broad s, ^{1}H, NOH); 7.13–7.40 (m, 9H, CH_{arom}); 7.80 (d, J=7.5 Hz, ^{1}H, CH_{arom}); 8.09 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 18.5 (CH_3); 59.1 (CHN); 61.1 (CH_2); 111.1 (CH); 117.0 (C); 119.5 (CH); 120.2 (CH); 122.0 (CH); 122.5 (CH); 126.7 (C); 127.0 (CH); 128.1 (CH); 129.4 (CH); 136.2 (C); 138.6 (C). MS (CI, NH_3+isobutane): m/z 267 (MH^+). Anal. calcd for $C_{17}H_{18}N_2O$: C: 76.66%, H: 6.81%, N: 10.52%; found C: 76.28%, H: 6.72%, N: 10.24%.

***N*-Benzyl-2-benzyloxy-*N*-hydroxy-1-(3′-indolyl)ethylamine (3da).** Yield: 88%. Mp: 49–51°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 3.76 (ABq, J_{AB}=13.7 Hz, $\delta_A-\delta_B$=26.1, 2H, NCH_2Ph); 3.81 (dd, J=5.1, 9.9 Hz, ^{1}H, ^{1}H of CH_2); 4.13 (dd, J=7.2, 9.9 Hz, ^{1}H, ^{1}H of CH_2); 4.42 (dd, J=5.1, 7.2 Hz, ^{1}H, CHN); 4.52 (s, 2H, OCH_2Ph); 5.68 (s, ^{1}H, NOH); 7.10–7.32 (m, 14H, CH_{arom}); 7.65 (d, J=7.2 Hz, ^{1}H, CH_{arom}); 8.21 (broad s, ^{1}H, NH). ^{13}C ($CDCl_3$, 50.3 MHz): 61.7 (CH_2); 63.0 (CHN); 72.1 (CH_2); 73.1 (CH_2); 108.9 (C); 111.2 (CH); 111.9 (C); 119.7 (CH); 119.8 (CH); 122.1 (CH); 123.8 (CH); 127.0 (CH); 127.6 (CH); 127.7 (CH); 128.1 (CH); 128.3 (CH); 129.3 (CH); 136.0 (C); 138.2 (C); 138.4 (C). MS (CI, NH_3+isobutane): m/z 373 (MH^+). Anal. calcd for $C_{24}H_{24}N_2O_2$: C: 77.42%, H: 6.45%, N: 7.53%; found: C: 77.11%, H: 6.45%, N: 7.26%.

***N*-Benzyl-2-*tert*-butoxycarbonylamino-*N*-hydroxy-1-(3′-indolyl)ethylamine (3ea).** Yield: 95%. Mp: 145–146°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.51 (s, 9H, $C(CH_3)_3$); 3.50–3.70 (m, 2H, CH_2N); 3.75 (ABq, J_{AB}=14.4 Hz, $\delta_A-\delta_B$=38.9, 2H, CH_2Ph); 4.14 (nearly t, J=5.5, 5.8 Hz, ^{1}H, CHN); 4.88 (t, J=6.5 Hz, ^{1}H, NHBoc); 6.56 (broad s, ^{1}H, NOH); 7.08–7.39 (m, 9H, CH_{arom}); 7.66 (d, J=7.5 Hz, ^{1}H, CH_{arom}); 8.36 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.5 ($C(CH_3)_3$); 43.7 (CH_2); 60.6 (CH_2); 63.8 (CHN); 79.7 ($C(CH_3)_3$); 111.2 (CH); 112.3 (C); 119.6 (CH); 119.7 (CH); 122.2 (CH); 123.4 (CH); 126.7 (CH); 127.2 (C); 128.0 (CH); 128.6 (CH); 136.0 (C); 139.0 (C); 157.7 (CO_2). MS (CI, NH_3+isobutane): m/z 382 (MH^+). Anal. calcd for $C_{22}H_{27}N_3O_3$: C: 69.27%, H: 7.13%, N: 11.01%; found: C: 69.23%, H: 7.36%, N: 10.77%.

***N*-Benzyl-*N*-hydroxy-1-(3′-indolyl)-1-(*p*-nitrophenyl)-methylamine (3ga).** Yield: 44%. Mp: 87–89°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.55–3.70 (m, 2H, CH_2); 3.72 (ABq, J_{AB}=14.0 Hz, $\delta_A-\delta_B$=57.8, 2H, CH_2Ph); 4.07 (t, J=5.7 Hz, ^{1}H, CHN); 4.78–4.91 (nearly t, ^{1}H, NHBoc); 6.52 (broad s, ^{1}H, NOH); 7.18–7.35 (m, 7H, CH_{arom}); 7.51–7.55 (m, 2H, CH_{arom}); 8.22 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 61.8 (CH_2); 68.7 (CHN); 111.4 (CH); 114.5 (C); 119.6 (CH); 119.8 (CH); 120.2 (CH); 122.7 (CH); 123.5 (CH); 123.6 (CH); 126.1 (C); 127.3 (C); 128.3 (CH); 128.6 (CH); 129.2 (CH); 136.3 (C); 146.8 (C); 150.1 (C). MS (CI, NH_3+isobutane): m/z 374 (MH^+). Anal. calcd for $C_{22}H_{19}N_3O_3$: C: 70.78%, H: 5.09%, N: 11.26%; found: C: 71.03%, H: 5.29%, N: 10.99%.

***N*-Benzyl-*N*-hydroxy-1-(5′-methoxy-3′-indolyl)propylamine (3ab).** Yield: 83%. Mp: 136–137°C. ^{1}H NMR (d_6 acetone, 200 MHz): 0.83 (t, J=7.3 Hz, 3H, CH_3); 1.84–2.04 (m, ^{1}H, ^{1}H of CH_2); 2.04–2.35 (m, ^{1}H, ^{1}H of CH_2); 2.81 (s, ^{1}H, NOH); 3.66 (ABq, J_{AB}=14.0 Hz, $\delta_A-\delta_B$=53.4, 2H, CH_2Ph); 3.79 (s, 3H, OCH_3); 3.80–3.91 (m, ^{1}H, CHN); 6.72–6.82 (m, 2H, CH_{arom}); 7.10–7.32 (m, 7H, CH_{arom}); 9.97 (broad s, ^{1}H, NH). ^{13}C NMR (d_6 acetone, 50.3 MHz): 11.7 (CH_3); 26.9 (CH_2); 55.8 (OCH_3); 62.2 (CH_2); 67.8

(CHN); 102.8 (CH); 112.4 (CH); 112.7 (CH); 115.3 (C); 125.1 (C); 125.3 (CH); 127.1 (CH); 128.5 (CH); 129.8 (CH); 132.9 (C); 141.1 (C); 154.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 311 (MH^+). Anal. calcd for $C_{19}H_{22}N_2O_2$: C: 73.52%, H: 7.14%, N: 9.03%; found: C: 73.60%, H: 7.19%, N: 9.09%.

***N*-Benzyl-*N*-hydroxy-1-(5′-methoxy-3′-indolyl)ethylamine (3bb).** Yield: 88%. Mp: 134–135°C. ^{1}H NMR (d_6 acetone, 300 MHz): 1.59 (d, *J*=6.7 Hz, 3H, CH_3); 2.89 (s, ^{1}H, NOH); 3.70 (ABq, J_{AB}=14.0 Hz, $\delta_A-\delta_B$=45.8, 2H, CH_2Ph); 3.80 (s, 3H, OCH_3); 4.22 (q, *J*=6.7 Hz, ^{1}H, CHN); 6.72–6.78 (m, ^{1}H, CH_{arom}); 6.82 (s, ^{1}H, CH_{arom}); 7.09–7.37 (m, 7H, CH_{arom}); 9.94 (broad s, ^{1}H, NH). ^{13}C NMR (d_6 acetone, 75.5 MHz): 19.0 (CH_3); 55.8 (OCH_3); 60.9 (CHN); 61.4 (CH_2); 102.8 (CH); 112.5 (CH); 112.7 (CH); 119.1 (C); 124.3 (CH); 127.1 (CH); 128.0 (C); 128.5 (CH); 129.8 (CH); 132.9 (C); 141.1 (C); 154.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 297 (MH^+). Anal. calcd for $C_{18}H_{20}N_2O_2$: C: 72.97%, H: 7.76%, N: 9.46%; found: C: 73.23%, H: 7.71%, N: 9.49%.

***N*-Benzyl-2-benzyloxy-*N*-hydroxy-1-(5′-methoxy-3′-indolyl)ethylamine (3db).** Yield: 93%. Mp: 44–46°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 3.74 (s, 3H, OCH_3); 3.77 (ABq, J_{AB}=13.5 Hz, $\delta_A-\delta_B$=55.9, 2H, NCH_2Ph); 3.79 (dd, *J*=5.0, 10.0 Hz, ^{1}H, ^{1}H of CH_2); 4.12 (dd, *J*=7.0, 10.0 Hz, ^{1}H, ^{1}H of CH_2); 4.34 (dd, *J*=5.0, 7.0 Hz, ^{1}H, CHN); 4.48 (ABq, J_{AB}=12.0 Hz, δ_A-δ_B=9.8, 2H, OCH_2Ph); 6.03 (broad s, ^{1}H, NOH); 6.81 (dd, *J*=2.5, 9.0 Hz, ^{1}H, CH_{arom}); 7.01 (d, *J*=2.5 Hz, ^{1}H, CH_{arom}); 7.05 (d, *J*=2.5 Hz, ^{1}H, CH_{arom}); 7.09 (d, *J*=9.0 Hz, ^{1}H, CH_{arom}); 7.16–7.28 (m, 10H, CH_{arom}); 8.25 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 55.7 (OCH_3); 61.5 (CH_2); 62.5 (CHN); 71.9 (CH_2); 73.0 (CH_2); 101.5 (CH); 111.3 (C); 111.9 (CH); 112.3 (CH); 124.7 (CH); 126.9 (CH); 127.5 (CH); 127.6 (CH); 128.0 (CH); 128.2 (CH); 129.4 (CH); 131.1 (C); 138.2 (C); 153.9 (C). MS (CI, NH_3+isobutane): *m*/*z* 403 (MH^+). Anal. calcd for $C_{25}H_{26}N_2O_3$: C: 74.63%, H: 6.47%, N: 6.96%; found: C: 74.41%, H: 6.54%, N: 6.93%.

***N*-Benzyl-2-*tert*-butoxycarbonylamino-*N*-hydroxy-1-(5′-methoxy-3′-indolyl)ethylamine (3eb).** Yield: 95%. Mp: 141–143°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.51 (s, 9H, $C(CH_3)_3$); 3.46–3.78 (m, 2H, CH_2); 3.78 (ABq, J_{AB}=14.1 Hz, $\delta_A-\delta_B$=47.7, 2H, CH_2Ph); 3.83 (s, 3H, OCH_3); 4.09 (t, *J*=5.5 Hz, ^{1}H, CHN); 4.92 (t, *J*=5.5 Hz, ^{1}H, NHBoc); 6.58 (broad s, ^{1}H, NOH); 6.87 (dd, *J*=2.4, 8.9 Hz, ^{1}H, CH_{arom}); 7.10 (d, *J*=2.4 Hz, ^{1}H, CH_{arom}); 7.20–7.33 (m, 7H, CH_{arom}); 8.18 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.4 ($C(CH_3)_3$); 43.8 (CH_2); 55.9 (OCH_3); 60.6 (CH_2); 63.7 (CHN); 79.7 ($C(CH_3)_3$); 101.5 (CH); 111.9 (CH); 112.5 (CH); 124.2 (CH); 126.7 (CH); 127.5 (C); 128.0 (CH); 128.6 (CH); 131.2 (C); 139.0 (C); 154.1 (C); 157.7 (CO_2). MS (CI, NH_3+isobutane): *m*/*z* 412 (MH^+). Anal. calcd for $C_{23}H_{29}N_3O_4$: C: 67.15%, H: 7.06%, N: 10.22%; found: C: 67.15%, H: 7.36%, N: 10.09%.

***N*-Benzyl-1-(5′-bromo-3′-indolyl)-*N*-hydroxypropylamine (3ac).** Yield: 70%. Mp: 159–160°C. ^{1}H NMR (d_6 acetone, 300 MHz): 0.84 (t, *J*=7.4 Hz, 3H, CH_3); 1.85–1.95 (m, ^{1}H, ^{1}H of CH_2); 2.21–2.38 (m, ^{1}H, ^{1}H of CH_2); 2.81 (s, ^{1}H, NOH); 3.64 (ABq, J_{AB}=13.5 Hz, $\delta_A-\delta_B$=54.7, 2H, CH_2Ph); 3.90 (dd, *J*=5.2, 8.9 Hz, ^{1}H, CHN); 6.89 (s, ^{1}H, CH_{arom}); 7.13–7.45 (m, 8H, CH_{arom}); 7.98 (broad s, ^{1}H, NH). ^{13}C NMR (d_6 acetone, 75.5 MHz): 11.0 (CH_3); 26.3 (CH_2); 61.5 (CH_2); 66.7 (CHN); 111.7 (C); 113.3 (CH); 114.7 (C); 123.1 (CH); 124.0 (CH); 125.7 (CH); 126.5 (CH); 127.9 (CH); 129.2 (CH); 129.4 (C); 135.8 (C); 140.1 (C). MS (CI, NH_3+isobutane): *m*/*z* 359 and 361 (MH^+).

***N*-Benzyl-1-(5′-bromo-3′-indolyl)-*N*-hydroxyethylamine (3bc).** Yield: 82%. Mp: 106–107°C. ^{1}H NMR (d_6 acetone, 250 MHz): 1.60 (d, *J*=6.3 Hz, 3H, CH_3); 2.94 (s, ^{1}H, NOH); 3.68 (ABq, J_{AB}=13.5 Hz, $\delta_A-\delta_B$=41.5, 2H, CH_2Ph); 4.24 (q, *J*=6.3 Hz, ^{1}H, CHN); 6.99 (broad s, ^{1}H, CH_{arom}); 7.13–7.37 (m, 7H, CH_{arom}); 8.04 (s, ^{1}H, CH_{arom}); 10.32 (broad s, ^{1}H, NH). ^{13}C NMR (d_6 acetone, 62.5 MHz): 18.5 (CH_3); 60.3 (CHN); 61.0 (CH_2); 112.1 (C); 113.7 (CH); 117.7 (C); 123.5 (CH); 124.4 (CH); 125.1 (CH); 127.0 (CH); 128.3 (CH); 129.3 (C); 129.6 (CH); 136.2 (C); 140.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 345 and 347 (MH^+). Anal. calcd for $C_{17}H_{17}BrN_2O$: C: 59.14%, H: 4.96%, N: 8.11%; found: C: 58.96%, H: 5.00%, N: 7.81%.

***N*-Benzyl-1-(5′-bromo-3′-indolyl)-2-*tert*-butoxycarbonylamino-*N*-hydroxyethylamine (3ec).** Yield: 83%. Mp: 170–171°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.53 (s, 9H, $C(CH_3)_3$); 3.47–3.73 (m, 2H, CH_2); 3.71 (ABq, J_{AB}=14.1 Hz, $\delta_A-\delta_B$=43.0, 2H, CH_2Ph); 4.03 (t, *J*=5.5 Hz, ^{1}H, CHN); 4.89 (nearly t, *J*=6.9 Hz, ^{1}H, NHBoc); 6.73 (broad s, ^{1}H, NOH); 7.15–7.50 (m, 8H, CH_{arom}); 7.83 (s, ^{1}H, CH_{arom}); 8.42 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.4 ($C(CH_3)_3$); 44.0 (CH_2); 60.6 (CH_2); 63.9 (CHN); 80.0 ($C(CH_3)_3$); 112.2 (C); 112.7 (CH); 113.0 (C); 122.5 (CH); 124.6 (CH); 125.1 (CH); 126.8 (CH); 128.0 (CH); 128.6 (CH); 128.8 (C); 134.7 (C); 138.7 (C); 157.7 (CO_2). MS (CI, NH_3+isobutane): *m*/*z* 460 and 462 (MH^+). Anal. calcd for $C_{22}H_{26}BrN_3O_3$: C: 57.39%, H: 5.65%, N: 9.13%; found: C: 57.07%, H: 5.65%, N: 9.22%.

***N*-Benzyl-1-(6′-bromo-3′-indolyl)-2-*tert*-butoxycarbonylamino-*N*-hydroxyethylamine (3ed).** Yield: 78%. Mp: 159–160°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.50 (s, 9H, $C(CH_3)_3$); 3.55–3.70 (m, 2H, CH_2); 3.72 (ABq, J_{AB}=14.0 Hz, $\delta_A-\delta_B$=57.8, 2H, CH_2Ph); 4.07 (t, *J*=5.7 Hz, ^{1}H, CHN); 4.78–4.91 (nearly t, ^{1}H, NHBoc); 6.52 (broad s, ^{1}H, NOH); 7.18–7.35 (m, 7H, CH_{arom}); 7.51–7.55 (m, 2H, CH_{arom}); 8.22 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 28.4 ($C(CH_3)_3$); 43.9 (CH_2); 60.5 (CH_2); 63.2 (CHN); 79.9 ($C(CH_3)_3$); 112.2 (C); 114.2 (CH); 115.8 (C); 120.9 (CH); 122.9 (CH); 124.1 (CH); 126.0 (C); 126.8 (CH); 128.1 (CH); 128.5 (CH); 136.7 (C); 138.8 (C); 157.7 (CO_2). MS (CI, NH_3+isobutane): *m*/*z* 460 and 462 (MH^+). Anal. calcd for $C_{22}H_{26}BrN_3O_3$: C: 57.39%, H: 5.69%, N: 9.13%; found: C: 57.09%, H: 5.87%, N: 9.05%.

Diastereoselective condensations

The reaction conditions were similar to those reported for the synthesis of other hydroxylamines **3** (4 h, 0°C). Starting with nitrone **1h** (0.224 g, 0.696 mmol), indole (0.081 g, 0.696 mmol), acetyl chloride (0.109 g, 1.39 mmol) and

methanol (7 mL), the two diastereoisomers (*R*,*R*)-**3ha** and (*S*,*R*)-**3ha** were isolated after column chromatography (silica gel, ethyl acetate/pentane; 1:9) in 62.5% (0.191 g, 0.435 mmol) and 5.5% (0.017 g, 0.0387 mmol) yields, respectively.

(R,R)-**3ha***:* Yield: 62.5%. Mp: 73–76°C. $[\alpha]_D^{20}=-31.4$ (c=1.08; chloroform). ^{1}H NMR (d_8 toluene, 300 MHz, 343 K): 1.30 (broad s, 9H, C(CH_3)$_3$); 2.86 (dd, J=7.0, 9.0 Hz, ^{1}H, ^{1}H of SCH_2); 3.14 (pseudo d, J=9.0 Hz, ^{1}H, ^{1}H of SCH_2); 3.72 (ABq, J_{AB}=13.5 Hz, $\delta_A-\delta_B$=77.4, 2H, CH_2Ph); 4.10 (ABq, J_{AB}=9.0 Hz, δ_A-δ_B=273.9, 2H, NCH_2S); 4.17 (d, J=6.0 Hz, ^{1}H, C*H*NOH); 5.27 (broad s, ^{1}H, CHNBoc); 6.37 (broad s, ^{1}H, NOH); 6.98–7.30 (m, 7H, CH_{arom}); 7.14 (d, J=7.0 Hz, ^{1}H, CH_{arom}); 7.23 (d, J=7.5 Hz, ^{1}H, CH_{arom}); 7.39 (broad s, ^{1}H, NH); 7.72 (d, J=7.0 Hz, ^{1}H, CH_{arom}). ^{13}C NMR (d_8 toluene, 75.5 MHz, 343 K): 28.4 (C(*C*H_3)$_3$); 33.6 (CH_2); 49.4 (CH_2); 62.0 (CH); 62.3 (CH_2); 67.0 (CH); 80.6 (*C*(CH_3)$_3$); 111.0 (C); 111.5 (CH); 120.1 (CH); 120.5 (CH); 122.4 (CH); 125.0 (CH); 127.0 (CH); 128.3 (CH); 128.8 (C); 129.6 (CH); 136.8 (C); 139.6 (C); 154.9 (CO_2). MS (CI, NH_3+isobutane): m/z 440 (MH^+). Anal. calcd for $C_{24}H_{29}N_3O_3S$: C: 65.60%, H: 6.61%, N: 9.57%, S: 7.29%; found: C: 65.43%, H: 6.59%, N: 9.39%, S: 7.21%.

Crystal structure: Single crystals were obtained by slow evaporation of a solution of (*R*,*R*)-**3ha** in ethanol. A crystal of 0.50×0.40×0.32 mm^3 was used for the crystallographic study. The unit-cell dimensions, a=13.283(3) and c=48.318(15) Å were refined by a least squares method from a set of 25 reflexions measured in a range of 10–12°. The space group is $P3_221$ and Z=12. Intensity data were collected with an Enraf-Nonius four-circle CAD4 diffractometer operating with molybdenum radiation monochromatized with a graphite plate.[25] Measurements performed at room temperature with an ω-type scan in the range 2–23°(θ) led to a set of 3991 reflexions which, processed using the TeXsan software,[26] provided a set of 3940 independent ones ($R_{int.}$=0.02) used for the structure determination, itself performed using a direct method, SIR92.[27] All non-hydrogen atoms were refined anisotropically, hydrogen ones, isotropically. The final R value is 0.062 (R_w=0.058). During the structural investigation a molecule of ethanol was found in the atomic arrangement. Additional data are: Dx=1.22, μ=1.63 cm^{-1}, GOF=2.06. All calculations were performed using the TeXsan software[26] and the drawing with the ORTEP system.[28]

(S,R)-**3ha***:* Yield: 5.5%. Mp: 87–89°C. $[\alpha]_D^{20}=-2.4$ (c=1.06; chloroform). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.59 (broad s, 9H, C(CH_3)$_3$); 2.50 (d, J=11.3 Hz, ^{1}H, ^{1}H of SCH_2); 2.92 (dd, J=6.2, 11.3 Hz, ^{1}H, ^{1}H of SCH_2); 3.70 (ABq, J_{AB}=14.1 Hz, $\delta_A-\delta_B$=14.6, 2H, CH_2Ph); 4.27 (d, J=11.7 Hz, ^{1}H, C*H*NOH); 4.45 (ABq, J_{AB}=8.6 Hz, $\delta_A-\delta_B$=76.3, 2H, NCH_2S); 4.87–4.95 (m, ^{1}H, CHNBoc); 7.08–7.60 (m, 1^{1}H, CH_{arom} and NOH); 8.36 (broad s, ^{1}H, NH).

We were unable to isolate compound **3ia** in pure form. Spectroscopic data obtained from impure **3i** are the following: ^{1}H NMR ($CDCl_3$, 300 MHz): 1.52 (broad s, 3H, CH_3); 1.56 (broad s, 3H, CH_3); 1.61 (broad s, 9H, C(CH_3)$_3$); 3.49 (d, J=8.9 Hz, ^{1}H, ^{1}H of OCH_2); 3.70 (ABq, J_{AB}=14.1 Hz, $\delta_A-\delta_B$=19.4, 2H, CH_2Ph); 3.70–3.74 (m, ^{1}H, ^{1}H of OCH_2); 4.07 (d, J=10.3 Hz, ^{1}H, C*H*NOH); 4.39–4.53 (m, ^{1}H, CHNBoc); 7.03–7.67 (m, 1^{1}H, CH_{arom} and NOH); 8.43 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 24.7 (CH_3); 27.7 (CH_3); 28.5 (C(*C*H_3)$_3$); 56.3 (CH); 60.3 (CH_2); 62.8 (CH); 65.9 (CH_2); 80.9 (*C*(CH_3)$_3$); 94.0 (*C*(CH_3)$_2$); 110.2 (C); 111.1 (CH); 119.6 (CH); 121.8 (CH); 124.7 (CH); 126.7 (CH); 127.8 (CH); 128.6 (CH); 135.4 (C); 136.7 (C); 138.8 (C); 154.7 (CO_2). MS (CI, NH_3+isobutane): m/z 452 (MH^+).

Condensations on position 2 of indole

These reactions were performed under an argon atmosphere. Typical experimental procedure: to a solution of indole (0.351 g, 3 mmol) in dry THF (6 mL), cooled at −78°C was added a solution of *n*-butyllithium in hexane (1.6 M, 2.06 mL, 3.3 mmol). The reaction mixture was stirred for 30 min before addition of excess dry ice. After another 5 min at −78°C and 30 min at r.t., the solvent and the excess of CO_2 were evaporated. The resulting white solid was dissolved in THF (6 mL). The obtained solution was cooled to −78°C and *t*-butyllithium (1.7 M in hexane, 1.94 mL, 3.3 mmol) was added. The reaction mixture was then stirred for 1.5 h at −78°C and transferred via syringe onto a suspension of nitrone **1a** (0.49 g, 3 mmol) in THF (6 mL) previously cooled to −78°C. After 2 h stirring, the reaction was quenched by water (0.22 mL) and the reaction mixture was warmed to r.t. A saturated aqueous solution of NH_4Cl was then added. The aqueous phase was extracted three times with CH_2Cl_2. The collected organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate/pentane: 5/95) to yield hydroxylamine **6a** as a white solid (0.483 g, 1.73 mmol).

***N*-Benzyl-*N*-hydroxy-1-(2′-indolyl)propylamine (6a).** Yield: 58%. Mp: 119–121°C. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.90 (t, J=7.5 Hz, 3H, CH_3); 1.78–2.14 (m, 2H, CH_2); 3.66 (ABq, J_{AB}=13.0 Hz, $\delta_A-\delta_B$=18.9, 2H, CH_2Ph); 3.78 (dd, J=6.2, 8.6 Hz, ^{1}H, CHN); 5.85 (broad s, ^{1}H, NOH); 6.38 (d, J=1.4 Hz, ^{1}H, CH_{arom}); 7.08 (dd, J=1.4, 7.2 Hz, ^{1}H, CH_{arom}); 7.14 (dd, J=1.7, 2.4 Hz, ^{1}H, CH_{arom}); 7.20 (dd, J=1.4, 7.2 Hz, ^{1}H, CH_{arom}); 7.25–7.45 (m, 5H, CH_{arom}); 7.60 (d, J=7.5 Hz, ^{1}H, CH_{arom}); 8.73 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 11.3 (CH_3); 25.6 (CH_2); 60.9 (CH_2); 66.0 (CHN); 102.8 (CH); 110.9 (CH); 119.5 (CH); 120.2 (CH); 121.6 (CH); 127.4 (CH); 127.6 (C); 128.3 (CH); 129.7 (CH); 136.3 (C); 136.9 (C); 137.5 (C). MS (CI, NH_3+isobutane): m/z 281 (MH^+). Anal. calcd for $C_{18}H_{20}N_2O$: C: 77.11%, H: 7.19%, N: 9.99%; found: C: 76.89%, H: 7.20%, N: 9.83%.

***N*-Benzyl-*N*-hydroxy-1-(2′-indolyl)ethylamine (6b).** Yield: 36%. ^{1}H ($CDCl_3$, 200 MHz): 1.44 (d, J=6.9 Hz, 3H, CH_3); 3.55 (ABq, J_{AB}=13.0 Hz, $\delta_A-\delta_B$=23.0, 2H, CH_2Ph); 3.97 (q, J=6.9 Hz, ^{1}H, CHN); 6.28 (broad s, ^{1}H, CH_{arom}); 6.47 (broad s, ^{1}H, NOH); 7.00 (dd, J=1.4, 7.2 Hz, ^{1}H, CH_{arom}); 7.05–7.26 (m, 6H, CH_{arom}); 7.30 (d, J=8.2 Hz, ^{1}H, CH_{arom}); 7.52 (d, J=7.2 Hz, ^{1}H, CH_{arom}); 8.67 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 17.1 (CH_3); 59.5 (CHN); 60.0

(CH_2); 101.3 (CH); 110.9 (CH); 119.6 (CH); 120.3 (CH); 121.7 (CH); 127.5 (CH); 127.8 (C); 128.3 (CH); 129.7 (CH); 136.3 (C); 137.5 (C); 138.8 (C). MS (CI, NH_3+isobutane): *m*/*z* 267 (MH^+). Anal. calcd for $C_{17}H_{18}N_2O$: C: 76.66%, H: 6.81%, N: 10.52%; found: C: 76.37%, H: 6.80%, N: 10.26%.

Synthesis of naturally occurring diindolylalkanes

Streptindole (7). To a solution of **4da** (0.127 g, 0.347 mmol) in dry methanol (5 mL) were added acetic acid (0.2 mL) and Pearlman reagent ($Pd(OH)_2$/C, 0.052 g). The reaction mixture was stirred under a H_2 atmosphere for 18 h and then filtered through celite. The solvents were removed under vacuum. The obtained crude product was dissolved in ethyl acetate and treated with $NaHCO_3$ until basic pH. After extraction (EtOAc, three times), washing of the organic phase with brine, drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent, the crude product was purified by column chromatography (silica gel, diethyl ether) to yield the expected alcohol[17] in 95% yield (0.091 g, 0.33 mmol). This alcohol (0.050 g, 0.18 mmol) was stirred in acetic anhydride (2 mL) in the presence of sodium acetate (0.060 g, 0.73 mmol) for 17 h. Ethyl acetate (1.4 mL) and ethanol (0.2 mL) were then added and the resulting mixture was stirred for 24 h. The mixture was washed three times (first water, then aqueous solution of $NaHCO_3$, then brine). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give the crude acetate which was purified by preparative TLC (silica gel, diethyl ether/pentane; 1:1). Streptindole **7** was isolated in 83% yield (0.048 g, 0.151 mmol). Its IR and ^{1}H NMR spectra were in agreement with those previously reported.[17] Anal. calcd for $C_{20}H_{18}N_2O_2$: C: 75.47%, H: 5.66%, N: 8.80%; found: C: 75.32%, H: 5.65%, N: 8.73%.

2,2-Bis(6′-bromo-3′-indolyl)ethylamine (8). This compound was obtained by treatment of its *N*-Boc-protected precursor **4ed** (0.054 g, 0.1 mmol) with trifluoroacetic acid (0.1 M solution in CH_2Cl_2, 1 mL) at r.t. The reaction was monitored by TLC (silica gel, ethyl acetate/hexane; 3:7) and was finished after 2 h. The reaction mixture was then diluted with ethyl acetate and treated with a saturated aqueous solution of $NaHCO_3$ until the pH became basic. The aqueous layer was extracted three times with ethyl acetate. The collected organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated under vacuum and the crude product was purified by column chromatography to yield pure amine **8** (0.034 g, 0.078 mmol, 78% yield) as an amorphous solid. Its ^{1}H and ^{13}C NMR spectra were in agreement with those reported for the natural compound.[18] Anal. calcd for $C_{18}H_{15}Br_2N_3$: C: 49.91%, H: 3.49%; found: C: 49.89%, H: 3.55%.

Synthesis of non-symmetric diindolylalkanes

A solution of the hydroxylamine **3** (1 mmol) and freshly distilled $ClSiMe_3$ (1 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at r.t. for 5 min. The indole derivative **2** was then added and the reaction was monitored by TLC (silica gel, diethyl ether/pentane: 1/1) until completion. The reaction mixture was then treated with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted three times by CH_2Cl_2. The collected organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under vacuum and the obtained crude product was purified by column chromatography (ethyl acetate/hexane or ether/pentane).

1-(5′-Bromo-3′-indolyl)-1-(3″-indolyl)propane (9aac). Yield: 76%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 250 MHz): 0.96 (t, *J*=7.1 Hz, 3H, CH_3); 2.09–2.27 (m, 2H, CH_2); 4.26 (t, *J*=7.1 Hz, ^{1}H, CH); 6.87 (s, ^{1}H, CH_{arom}); 6.90 (s, ^{1}H, CH_{arom}); 6.90–7.21 (m, 4H, CH_{arom}); 7.28 (d, *J*=7.9 Hz, ^{1}H, CH_{arom}); 7.53 (d, *J*=7.9 Hz, ^{1}H, CH_{arom}); 7.69 (s, ^{1}H, CH_{arom}); 7.75 (broad s, ^{1}H, NH); 7.78 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 13.0 (CH_3); 28.4 (CH_2); 35.8 (CH); 111.1 (CH); 112.2 (C); 112.5 (CH); 118.9 (CH); 119.5 (CH); 119.8 (C); 121.4 (CH); 121.7 (CH); 122.0 (CH); 122.7 (CH); 124.4 (CH); 126.9 (C); 128.8 (C); 135.1 (C); 136.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 353 and 355 (MH^+), 352 and 354 (M^+). Anal. calcd for $C_{19}H_{17}BrN_2$: C: 64.60%, H: 4.85%, N: 7.93%; found: C: 64.87%, H: 5.03%, N: 7.65%.

1-(6′-Bromo-3′-indolyl)-1-(3″-indolyl)propane (9aad). Yield: 84%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 200 MHz): 0.99 (t, *J*=7.2 Hz, 3H, CH_3); 2.21 (quint., *J*=7.2 Hz, 2H, CH_2); 4.32 (t, *J*=7.2 Hz, ^{1}H, CH); 6.97–7.56 (m, 9H, CH_{arom}); 7.85 (broad s, ^{1}H, NH); 7.88 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 12.9 (CH_3); 28.5 (CH_2); 35.7 (CH); 111.1 (CH); 113.9 (CH); 115.2 (C); 119.0 (CH); 119.5 (CH); 120.8 (CH); 121.4 (CH); 121.8 (CH); 122.0 (CH); 122.2 (CH); 126.0 (C); 127.0 (C); 136.5 (C); 137.2 (C). MS (CI, NH_3+isobutane): *m*/*z* 353 and 355 (MH^+).

1-(3′-Indolyl)-1-(5″-methoxy-3″-indolyl)propane (9aab). Yield: 83%. ^{1}H NMR ($CDCl_3$, 250 MHz): 1.00 (t, *J*=7.1 Hz, 3H, CH_3); 2.22 (q, *J*=7.1 Hz, 2H, CH_2); 3.76 (s, 3H, OCH_3); 4.31 (t, *J*=7.1 Hz, ^{1}H, CH); 6.80 (dd, *J*=2.4, 8.7 Hz, ^{1}H, CH_{arom}); 6.93 (broad s, 2H, CH_{arom}); 6.99–7.23 (m, 4H, CH_{arom}); 7.29 (d, *J*=7.9 Hz, ^{1}H, CH_{arom}); 7.59 (d, *J*=7.9 Hz, ^{1}H, CH_{arom}); 7.73 (broad s, ^{1}H, NH); 7.83 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 13.1 (CH_3); 28.5 (CH_2); 35.8 (CH); 55.9 (OCH_3); 101.9 (CH); 111.0 (CH); 111.5 (CH); 111.6 (CH); 118.9 (CH); 119.6 (CH); 119.9 (C); 120.1 (C); 121.4 (CH); 121.6 (CH); 122.3 (CH); 127.2 (C); 127.6 (C); 131.7 (C); 136.6 (C); 153.5 (C). MS (CI, NH_3+isobutane): *m*/*z* 305 (MH^+). Anal. calcd for $C_{20}H_{20}N_2O$: C: 78.92%, H: 6.62%, N: 9.20%; found: C: 79.13%, H: 6.61%, N: 9.07%.

1-(3′-Indolyl)-1-(2″-methyl-3″-indolyl)propane (9aae). Yield: 74%. Mp: 156–158°C. ^{1}H NMR ($CDCl_3$, 250 MHz): 0.93 (t, *J*=7.1 Hz, 3H, CH_3); 2.12–2.48 (m, 2H, CH_2); 2.38 (s, 3H, CH_3); 4.29 (dd, *J*=5.5, 10.3 Hz, ^{1}H, CH); 6.94–7.13 (m, 5H, CH_{arom}); 7.21–7.30 (m, 2H, CH_{arom}); 7.42 (d, *J*=7.9 Hz, ^{1}H, CH_{arom}); 7.57 (d, *J*=7.1 Hz, ^{1}H, CH_{arom}); 7.65 (broad s, ^{1}H, NH); 7.84 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 12.2 (CH_3); 13.0 (CH_3); 27.5 (CH_2); 35.4 (CH); 110.0 (CH); 110.9 (CH); 113.8 (C); 118.6 (CH); 118.9 (CH); 119.4 (CH); 120.4 (CH); 120.7 (C); 121.0 (CH); 121.6 (CH); 127.3 (C); 128.1 (C); 131.0 (C); 135.3 (C); 136.4 (C). MS (DCI, NH_3+isobutane): *m*/*z* 288 (M^+). Anal. calcd for $C_{20}H_{20}N_2$:

C: 83.33%, H: 6.94%, N: 9.72%; found: C: 83.60%, H: 6.89%, N: 9.59%.

1-(5′-Bromo-3′-indolyl)-1-(3″-indolyl)ethane (9bac). Yields: 51% from **3ba**; 53% from **3bc**. Amorphous solid. ^{1}H NMR ($CDCl_3$, 250 MHz): 1.73 (d, J=7.1 Hz, 3H, CH_3); 4.54 (q, J=7.1 Hz, ^{1}H, CH); 6.86 (s, ^{1}H, CH_{arom}); 6.89 (s, ^{1}H, CH_{arom}); 6.91–7.19 (m, 4H, CH_{arom}); 7.26 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.50 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.64 (s, ^{1}H, CH_{arom}); 7.69 (broad s, ^{1}H, NH); 7.72 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 21.4 (CH_3); 28.1 (CH); 109.9 (CH); 111.8 (C); 113.2 (CH); 118.9 (CH); 119.3 (CH); 119.7 (C); 121.0 (CH); 121.4 (CH); 121.7 (CH); 122.8 (CH); 124.1 (CH); 126.9 (C); 128.8 (C); 135.1 (C); 136.5 (C). MS (CI, NH_3+isobutane): m/z 340 (MH^+). Anal. calcd for $C_{18}H_{15}BrN_2$: C: 63.72%, H: 4.42%, N: 8.26%; found: C: 64.00%, H: 4.39%, N: 8.01%.

1-(3′-Indolyl)-1-(5″-methoxy-3″-indolyl)ethane (9bab). Yields: 63% from **3ba**; 57% from **3bb**. Mp: 54–56°C. ^{1}H NMR ($CDCl_3$, 250 MHz): 1.77 (d, J=7.1 Hz, 3H, CH_3); 3.74 (s, 3H, OCH_3); 4.59 (q, J=7.1 Hz, ^{1}H, CH); 6.80–6.83 (m, 3H, CH_{arom}); 7.00–7.20 (m, 4H, CH_{arom}); 7.27 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.56 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.67 (broad s, ^{1}H, NH); 7.77 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 21.5 (CH_3); 28.1 (CH); 55.9 (OCH_3); 101.7 (CH); 111.0 (CH); 111.7 (CH); 111.9 (CH); 118.9 (CH); 119.7 (CH); 121.1 (CH); 121.3 (C); 121.5 (C); 121.7 (CH); 122.0 (CH); 126.8 (C); 127.2 (C); 131.7 (C); 136.6 (C); 153.5 (C). MS (CI, NH_3+isobutane): m/z 291 (MH^+).

2-Benzyloxy-1-(5′-bromo-3′-indolyl)-1-(3″-indolyl)-ethane (9dac). Yield: 83%. ^{1}H NMR ($CDCl_3$, 250 MHz): 4.05 (d, J=7.1 Hz, 2H, CH_2); 4.53 (s, 2H, CH_2Ph); 4.77 (t, J=7.1 Hz, ^{1}H, CH); 6.80 (broad s, ^{1}H, CH_{arom}); 6.84 (broad s, ^{1}H, CH_{arom}); 7.01–7.14 (m, 4H, CH_{arom}); 7.19–7.23 (m, 5H, CH_{arom}); 7.32 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.56 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.72 (s, ^{1}H, CH_{arom}); 7.80 (broad s, ^{1}H, NH); 7.84 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 34.6 (CH); 72.8 (CH_2); 73.1 (CH_2); 109.6 (CH); 112.2 (C); 112.5 (CH); 119.0 (CH); 119.4 (CH); 119.7 (C); 121.2 (CH); 121.5 (CH); 122.1 (CH); 122.9 (CH); 124.3 (CH); 127.0 (C); 127.5 (CH); 127.7 (CH); 128.2 (CH); 128.7 (C); 131.5 (C); 136.4 (C); 138.2 (C). MS (CI, NH_3+isobutane): m/z 443 and 445 (M^+). Anal. calcd for $C_{25}H_{21}BrN_2O$: C: 67.42%, H: 4.72%, N: 6.29%; found: C: 67.23%, H: 4.71%, N: 6.23%.

2-Benzyloxy-1-(3′-indolyl)-1-(5″-methoxy-3″-indolyl)-ethane (9dab). Yield: 76%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 250 MHz): 3.69 (s, 3H, OCH_3); 4.09 (d, J=7.1 Hz, 2H, CH_2); 4.56 (s, 2H, CH_2Ph); 4.82 (t, J=6.3 Hz, ^{1}H, CH); 6.79 (dd, J=2.4, 6.7 Hz, ^{1}H, CH_{arom}); 6.81 (broad s, ^{1}H, CH_{arom}); 6.88 (broad s, ^{1}H, CH_{arom}); 6.96 (d, J=2.4 Hz, ^{1}H, CH_{arom}); 7.02 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.10–7.15 (m, 2H, CH_{arom}); 7.20–7.35 (m, 6H, CH_{arom}); 7.52 (d, J=7.9 Hz, ^{1}H, CH_{arom}); 7.77 (broad s, ^{1}H, NH); 7.89 (broad s, ^{1}H, NH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): 34.6 (CH); 55.8 (OCH_3); 72.9 (CH_2); 73.3 (CH_2); 101.4 (CH); 111.0 (CH); 111.7 (CH); 116.7 (C); 119.0 (CH); 119.5 (CH); 121.7 (CH); 122.4 (CH); 123.2 (CH); 127.0 (C); 127.3 (C); 127.5 (CH); 127.7 (CH); 128.2 (CH); 131.5 (C); 136.3 (C); 138.3 (C); 153.5 (C). MS (CI, NH_3+isobutane): m/z 396 (M^+). Anal. calcd for $C_{26}H_{24}N_2O_2$: C: 78.79%, H: 6.06%, N: 7.07%; found: C: 78.67%, H: 6.05%, N: 6.99%.

1-(6′-Bromo-3′-indolyl)-*N*-*tert*-butoxycarbonyl-1-(3″-indolyl)ethylamine (9ead). Yield: 48%. Amorphous solid. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.42 (s, 9H, $C(CH_3)_3$); 3.86 (t, J=6.5 Hz, 2H, CH_2); 4.56–4.73 (m, 2H, CH and NH); 6.92 (broad s, 2H, CH_{arom}); 6.95–7.57 (m, 7H, CH_{arom}); 8.11 (broad s, 2H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 28.4 ($C(CH_3)_3$); 34.5 (CH); 44.8 (CH_2); 79.3 ($C(CH_3)_3$); 111.2 (CH); 114.1 (CH); 115.5 (C); 116.6 (CH); 117.2 (C); 119.4 (CH); 120.8 (CH); 122.0 (CH); 122.1 (CH); 122.6 (CH); 125.8 (C); 126.7 (C); 136.5 (C); 137.3 (C); 156.1 (CO_2).

Acknowledgements

This work has been generously supported by the ‘Association pour la Recherche sur le Cancer’ (ARC).

References

1. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909; Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
2. Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495; Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759–1769; Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627–5630; Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629–646; Dondoni, A.; Perrone, D.; Rinaldi, M. *J. Org. Chem.* **1998**, *63*, 9252–9264.
3. (a) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 5503–5506. (b) Dagoneau, C.; Denis, J.-N.; Vallée, Y. *Synlett* **1999**, 602–604.
4. Denis, J.-N.; Mauger, H.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 8515–8518.
5. Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3157–3165.
6. Miyano, S.; Mibu, N.; Irie, M.; Fujii, S.; Fujisaki, F.; Abe, N.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 313–316.
7. Smith, G. F. *Chem. Ind.* **1954**, 1451–1452.
8. Tepe, J. J.; Madalengoitia, J. S.; Slunt, K. M.; Werbovetz, K. W.; Spoors, P. G.; Macdonald, T. L. *J. Med. Chem.* **1996**, *39*, 2188–2196.
9. Rinehart Jr, K. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387 and references therein.
10. Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935–5938.
11. Sundberg, R. J. *The Chemistry of Indoles*, Academic Press: New York, 1970.
12. Kamal, A.; Qureshi, A. A. *Tetrahedron* **1963**, *19*, 513–520.
13. Concerning the use of lanthanide triflates, see: Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467–4470.
14. Bell, R.; Carmeli, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587–1590.
15. Osawa, T.; Namiki, M.; Suzuki, K.; Mitsuoka, T. *Mutation Res.* **1983**, *122*, 299–304.
16. Osawa, T.; Namiki, M. *Tetrahedron Lett.* **1983**, *24*, 4719–4722.

17. Hogan, I. T.; Sainsbury, M. *Synthesis* **1984**, 872.
18. Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564–569.
19. Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. *J. Nat. Prod.* **1995**, *58*, 1254–1260.
20. Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537–2550.
21. Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 5834–5840.
22. Asrof Ali, Sk.; Azhar Hashmi, S. M.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917–14928.
23. Murray, R. W.; Singh, M. *J. Org. Chem.* **1990**, *55*, 2954–2957.
24. Suda, K.; Takanami, T. *Chem. Lett.* **1994**, 1915–1916.
25. Enraf-Nonius. CAD-4 Software. Enraf-Nonius, Delft, The Netherlands, 1992.
26. Molecular Structure Corporation, TeXsan: Single Crystal Structure Analysis Software, Version 1.7. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1995.
27. Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D. *J. Appl. Cryst.* **1989**, *22*, 389–393.
28. Johnson, C.K. ORTEP II. A Fortran Thermal Ellipsoid Plot Program, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, USA, 1976.