Solvent-Free Indoles Addition to Carbonyl Compounds Promoted by $CeCl_3 \cdot 7H_2O$–NaI–SiO_2: An Efficient Method for the Synthesis of Streptindole

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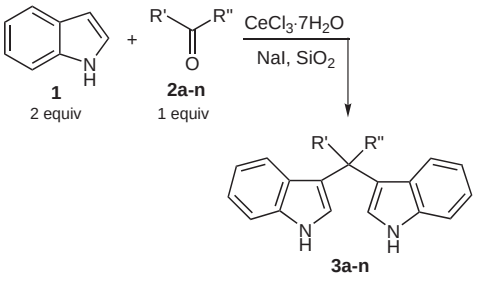
Abstract: Efficient electrophilic substitution reactions of indoles with various carbonyl compounds proceed easily in solvent-free conditions using $CeCl_3 \cdot 7H_2O$–NaI–SiO_2 system promoter, to afford the corresponding bis(1*H*-indol-3-yl)alkanes in high yields. The synthetic value of the present procedure is demonstrated by the synthesis of streptindole (**9**), human intestinal bacteria metabolite.

Key words: addition reactions, carbonyl complexes, indoles, lanthanides, Lewis acids, natural products

In the last years several researchers have reported many examples of new natural products in which the bis(1*H*-indol-3-yl)alkane structure is present.[1] This unit has been recently found to exhibit important biological activity,[2] and, therefore, the synthesis of these moieties has become an interesting target to synthetic organic chemists. In particular, there has been an interesting emphasis on pharmacological activity, and a direct synthesis of 3,3′-bis(indolyl)alkanes is desired.[1] The plethora of ingenious methods developed to obtain these bis(1*H*-indol-3-yl)alkane derivatives is a clear testimony to their paramount importance, and several procedures have been reported in the literature using Lewis acid[4] or protic acid[5] promoters for the addition of indole to carbonyl compounds. Unfortunately, most of these procedures require rather harsh acidic conditions, often incompatible[6] with other sensitive functions present in the substrates. In the last decade, milder protocols have emerged based upon the use of catalytic amounts of Lewis acids,[4e,f,7] but the long reaction time and complicated manipulation, along with the use of environmentally harmful organic solvents, limited their extension from the environmentally friendly viewpoint. More recently, these electrophilic substitution reactions of indoles with various aldehydes and ketones have been carried out using I_2 in organic solvents[7] or in ionic liquids without additional catalyst.[8] Thus, there is a general interest in a simple and efficient synthetic access to compounds containing a bis(1*H*-indol-3-yl)alkane moiety.

Although performing organic synthesis in an aqueous medium is a current challenge that will attract considerable attention in the coming years,[9] from the point of view of green chemistry it would be even more convenient to avoid the use of any solvent.[10] The solvent-free approach[11] is particularly appealing when one reagent is a liquid and available in large quantities, such as carbonyl compounds. Our studies in this area include Michael reactions of 1,3-dicarbonyl compounds[12] and amines[13] to α,β-enones. Lately, during the course of some synthetic studies directed towards the preparation of alkaloids embodying an indolyl moiety, we had the opportunity to examine the addition of indoles to electron-deficient alkenes promoted by a cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) and sodium iodide (NaI) combination supported on silica gel (SiO_2). Thus, due to the current challenge for developing solvent-free and environmentally benign synthetically systems[14] and to extend our interest in the applications of $CeCl_3 \cdot 7H_2O$ for various organic transformations,[15] we have described a simple, general and efficient protocol for the synthesis of β-indol-3-ylketones by Michael addition of indoles to α,β-enones.[16] However, in the case of α,β-unsaturated aldehydes the procedure suffers from regiochemical restriction caused by a competing 1,2- versus 1,4-addition. Attention was then focused on the use of the $CeCl_3 \cdot 7H_2O$–NaI system in the addition of indoles to saturated carbonyl compounds on a silica gel surface under solvent-free[17] conditions (Scheme 1).



Scheme 1

The addition reaction of indole (**1**) with isobutyraldehyde (**2a**) in the presence of 0.3 equivalents of cerium salt and 0.3 equivalents of NaI supported on SiO_2 (0.5 g/mmol carbonyl compound) proceeds well giving bis(1*H*-indol-3-yl)alkane **3a** in good yield for indole/aldehyde ratios larger than 2.0. The results are summarized in Table 1, which shows the addition reaction of aliphatic and aromatic aldehydes and ketones with indole in solvent-free conditions. Our initial observation has been that the indole

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nitrogen did not require protection. Furthermore, the data from entries 3–7 reflect the electronic effects of a substituent group at 4-position of aryl aldehydes towards the reaction. The consequences suggest that aromatic aldehydes with an electron-withdrawing substituent (i.e. NO_2, CF_3) react much faster than benzaldehyde or aldehydes with an electron-donating substituent (i.e. OCH_3), and again,[18] an opposite chemoselective outcome with respect to other Lewis acids[3] has been observed. Otherwise, the present reaction of indole with ketones required longer reaction times compared to aldehydes (entry 9). Also, the efficiency of the procedure is influenced by the ring size of cycloalkanones (entries 10 and 12), and the reaction fails with seven-membered ring ketones.

The use of a SiO_2 support facilitates the workup of the reaction mixture[19] and gave a better yield of products even though the reaction has also been observed in its absence. Presumably, silica gel acts as a carrier to increase the surface area in this heterogeneous reaction and it is very probable as well that the cerium salt interacts with hydroxyl or even oxide groups at the surface of the support forming new active sites with possible silica gel local structures. However, the fact that our methodology is clean and the adducts have been obtained in high yields without formation of any side products such as dimers or trimers, normally observed under the influence of strong acids,[20] exclude the existence in the solid of a distribution of sites containing simultaneously Brønsted and Lewis sites.[21] Furthermore, the $CeCl_3{\cdot}7H_2O$–NaI–SiO_2 system has been used for the addition of indole to benzaldehyde (**2c**) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine,[22] and, as expected, our Lewis acid promoter has afforded bis(1*H*-indol-3-yl)alkane **3c** in high yield and with absolute purity.

It should be noted that neither $CeCl_3$ nor NaI alone could effect the addition even after one week. Undoubtedly, the presence of NaI is essential for the reaction too. Therefore, a substoichiometric amount of the $CeCl_3{\cdot}7H_2O$–NaI system adsorbed on silica gel is an efficient Lewis acid promoter for the addition of indoles to carbonyl compounds, and the procedure allowed us to adopt a very simple workup process for the recovery of the bis(1*H*-indol-3-yl)alkane products. Indeed, the reaction mixture has been treated with an organic solvent (Et_2O) able to dissolve the organic material, while the $CeCl_3$–NaI silica gel support could be removed by filtration. Unfortunately, attempts to directly reuse the solid supported catalyst in a new addition reaction have been unsuccessful as catalytic activity is lost. The solid support, nevertheless, is regenerated by new treatment with the $CeCl_3{\cdot}7H_2O$–NaI combination, and the $CeCl_3{\cdot}7H_2O$–NaI–SiO_2 system prepared with used SiO_2 shows the same catalytic activity affording the adduct in almost identical yield.

Table 1 Addition of Indole **1** to Carbonyl Compounds Promoted by $CeCl_3{\cdot}7H_2O$–NaI (30%) Supported on SiO_2 at Room Temperature[a]

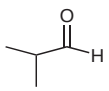
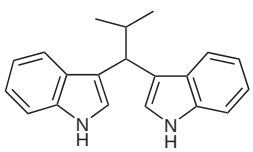
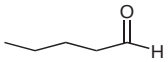
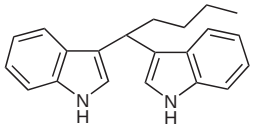
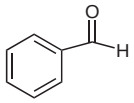
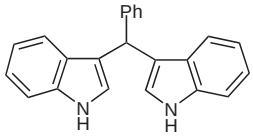
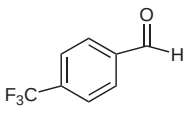
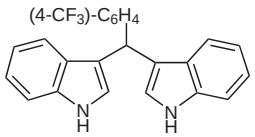
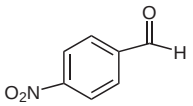
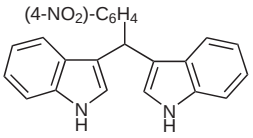
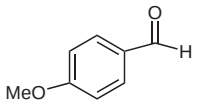
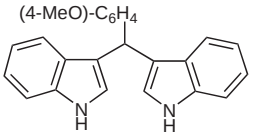
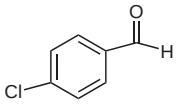
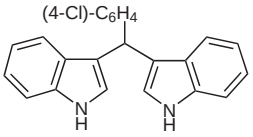
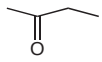
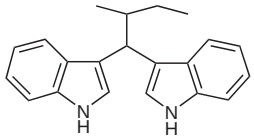
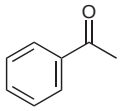
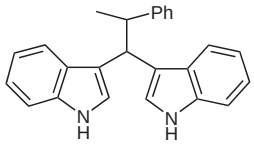
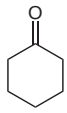
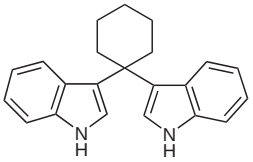
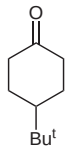
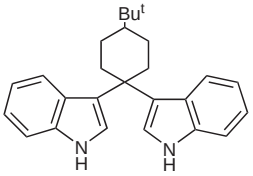
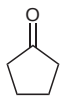
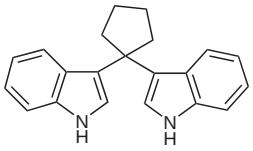
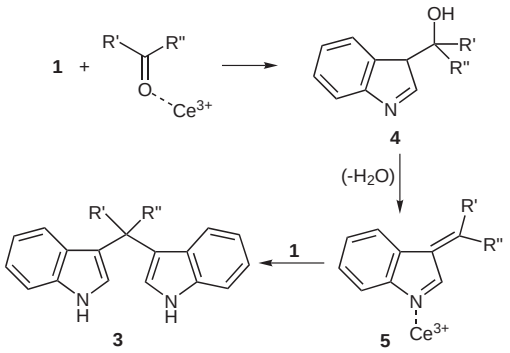
Entry	Carbonyl Compound	Time (h)	Product[b]	Yield (%)[c]
1	 **2a**	2	 **3a**	97
2	 **2b**	7	 **3b**	88
3	 **2c**	16	 **3c**	95
4	 **2d**	2.5	 **3d**	85

Table 1 Addition of Indole **1** to Carbonyl Compounds Promoted by $CeCl_3 \cdot 7H_2O$–NaI (30%) Supported on SiO_2 at Room Temperature[a] (continued)

Entry	Carbonyl Compound	Time (h)	Product[b]	Yield (%)[c]
5	 **2e**	5	 **3e**	78
6	 **2f**	21	 **3f**	80
7	 **2g**	12	 **3g**	70
8	 **2h**	32	 **3h**	76
9	 **2i**	140	 **3i**	21[d]
10	 **2l**	34	 **3l**	81
11	 **2m**	34	 **3m**	76
12	 **2n**	72	 **3n**	24[d]

[a] Reactions performed in the presence of 30 mol% of $CeCl_3 \cdot 7H_2O$ and 30 mol% of NaI supported on silica gel.
[b] All products were identified by their IR, NMR and GC/MS spectra.
[c] Yields of products isolated by column chromatography.
[d] Starting materials recovered.

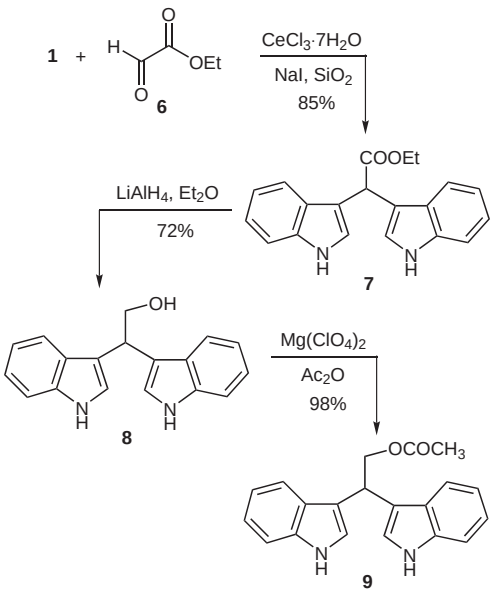
It has been observed that the substitution on the indole nucleus occurs exclusively at the 3-position. The fact that different ratios of reactants principally give bis(indolyl) adducts **3** led us to the suggestion that the reaction probably follows the pathway indicated in Scheme 2. The carbonyl compound is first activated by the Lewis acid promoter system, and carries out an electrophilic addition reaction at C-3 of the indole giving intermediate **4**. After loss of water, an azafulvene derivative **5** is generated which reacts further with a second molecule of indole to form bis(1*H*-indol-3-yl)alkanes **3**.



Scheme 2

Since the synthesis of bis(1*H*-indol-3-yl)alkanes constitutes an important reaction in organic synthesis and to evaluate better the usefulness of the present methodology, we focused our attention on the synthesis of a biologically active bis(indole), such as streptindole (**9**), for its broad range of pharmacological activity.[23] It has been isolated from intestinal bacteria *Streptococcus faecium* IB37 and causes DNA lesions in *Bacillus subtilis* cells. Previous syntheses of this genotoxic metabolite have been carried out by several groups, however, these routes are either laborious, comprised of steps of low yield, or require harsh reagents that may lead to degradation of the indole nucleus.[24,25] Consequently, we have been interested in preparing this compound, and we report thereafter an improved route to Streptindole by utilizing relatively eco-friendly reaction conditions. The strategy proceeds through known intermediates but via a new route and provides the highest overall yield of indole to date. For this purpose (Scheme 3), we started the reaction from indole (**1**) and ethyl glyoxylate (**6**) to give ethyl di-1*H*-indol-3-ylacetate (**7**) which is reduced to the corresponding alcohol **8** by action of lithium aluminium hydride. Finally, alcohol **8** is O-acetylated in the presence of a Lewis acid catalyst to afford streptindole (**9**). This acylation reaction is facilitated by the action of dried $Mg(ClO_4)_2$ as a useful alternative to metal triflate promoters.[26]

In conclusion, we have shown that bis(1*H*-indol-3-yl)alkanes can be synthesized by a simple and highly efficient addition of indoles to carbonyl compounds using a $CeCl_3 \cdot 7H_2O$–NaI combination supported on silica gel. The mildness of the reaction conditions and low cost of the reagents should make the present methodology synthetically useful. This search for new methods for the construction of organic molecules allows us to develop a new protocol for the synthesis of a natural product with biological activity. This result also suggests that the design of new synthetic applications should be possible, which will allow the already significant utility of cerium(III) salts to be developed further. Additional investigations of our Lewis acid promoter system in new schemes of synthesis for the preparation of other biologically important substances are in progress in our laboratories.



Scheme 3

All starting materials were commercial products. $CeCl_3 \cdot 7H_2O$ and NaI were purchased from Aldrich, and were used without further purification. All the obtained bis(1*H*-indol-3-yl)alkanes were characterized by IR, GC/MS, ^1H and ^{13}C NMR spectroscopy. Compounds **3a**,[25b] **3c**,[8] **3e**,[27] **3f**,[27] **3g**,[28] **3h**,[5b] **3i**,[5b] **3l**,[5e] and **3n**[5e] are all known and their structures were consistent with their published physical data. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR 300 spectrometer and referenced to the solvent as internal standard. Mass spectra were recorded on a Hewlett-Packard 5988 gas chromatography with a mass-selective detector MSD HP 5790 MS, utilizing electron ionization (EI) at an ionizing energy of 70 eV. Microanalyses were performed with a Perkin-Elmer Analyzer 2400 CHN. Infrared spectra were recorded on Perkin-Elmer FTIR Paragon 500 spectrometer using thin films on NaCl plates. Only the characteristic peaks are quoted. Analytical GC was performed with a capillary fused silica column (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.40–0.45 μm). Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a Baker silica gel (230–400 mesh) column using a EtOAc–hexanes mixture as eluent. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualized by UV light, Von's reagent, $KMnO_4$ or iodine staine.

Synthesis of bis(1*H*-Indol-3-yl)alkanes; Typical Procedure (Table 1, entry 1)

Silica gel (0.5 g) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.113 g, 0.3 mmol) and NaI (13.4 mg, 0.3 mmol) in CH_3CN (7 mL) and the mixture was stirred overnight at r.t. The solvent was removed and

to the resulting mixture was added indole (**1**, 0.234 g, 2 mmol) and isobutyraldehyde (**2a**, 0.072 g, 1 mmol). The reaction mixture was then stirred at r.t. until the disappearance of the starting indole (2 h, checked by TLC and GC analyses). After addition of Et_2O the mixture was passed through a short pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexanes, 25:75) to give 0.283 g (97% yield) of adduct **3a**.

3,3′-Pentane-1,1-diylbis-1*H*-indole (3b)
Colorless oil.

IR (neat): 3403, 1609, 1457 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.2 Hz), 1.27–1.44 (m, H), 2.15–2.45 (m, 2 H), 4.44 (t, 1 H, *J* = 8.0 Hz), 6.83–7.04 (m, 2 H), 7.17–7.50 (m, 8 H), 8.00 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 25.7, 30.1, 31.1, 36.0, 110.9, 116.3, 120.3, 121.0, 124.1, 125.6, 136.0, 138.3.

MS (EI, 70 eV): *m*/*z* (%) = 302 [M^+], 273, 245 (100), 186, 130, 116, 106, 57.

Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.42; H, 7.28; N, 9.23.

3,3′-{[4-(Trifluoromethyl)phenyl]methylene}bis-1*H*-indole (3d)
Colorless oil.

IR (neat): 3402, 1456, 1324 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.96 (s, 1 H), 6.65 (d, 2 H, *J* = 2.56 Hz), 7.04–7.08 (m, 2 H), 7.21–7.38 (m, 4 H), 7.83–7.91 (m, 5 H), 7.99–8.07 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.3, 110.7, 113.3, 117.8, 120.6, 121.0, 121.4, 122.8, 123.2, 125.7, 125.9, 127.5, 128.3, 131.2, 134.2, 140.7, 155.7.

MS (EI, 70 eV): *m*/*z* (%) = 390 [M^+, 100], 274, 245, 145, 116.

Anal. Calcd for $C_{24}H_{17}F_3N_2$: C, 73.84; H, 4.39; N, 7.18. Found: C, 73.81; H, 4.38; N, 7.23.

3,3′-(4-*tert*-Butylcyclohexane-1,1-diyl)bis-1*H*-indole (3m)
Colorless oil.

IR (neat): 3404, 1489 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 6 H), 0.93 (s, 3 H), 1.27–1.53 (m, 4 H), 1.71–1.76 (m, 1 H), 2.21–2.40 (m, 3 H), 2.91–2.98 (m, 1 H), 6.83–6.98 (m, 3 H), 7.04–7.19 (m, 2 H), 7.24–7.35 (m, 3 H), 7.49 (d, 1 H, *J* = 8.1 Hz), 7.67 (d, 1 H, *J* = 8.1 Hz), 7.77 (br s, 1 H), 8.02 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 28.4, 32.2, 38.5, 46.0, 51.0, 109.1, 117.2, 119.7, 120.3, 123.1, 124.8, 126.0, 140.3.

MS (EI, 70 eV): *m*/*z* (%) = 370 [M^+], 313, 271 (100), 130, 116, 57.

Anal. Calcd for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.32; H, 8.18; N, 7.53.

Ethyl Di-1*H*-indol-3-ylacetate (7)
To a combination of $CeCl_3 \cdot 7H_2O$ (0.143 g, 0.38 mmol) and NaI (17 mg, 0.38 mmol) supported on silica gel (1.92 g) prepared as described above was added indole (0.9 g, 7.68 mmol) and a 50% solution of ethyl glyoxylate (**6**) in toluene (0.75 mL, 3.84 mmol). The resulting mixture was stirred at r.t. until the disappearance of indole (48 h, checked by TLC analysis). Then Et_2O was added and the resulting mixture was concentrated. The crude product was purified by flash column chromatography (EtOAc–hexanes, 40:60) to give acetate **7** (1.04 g, 85% yield) as oil.

IR (neat): 3402, 1732, 1620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, 3 H, *J* = 7.1 Hz), 4.27 (q, 2 H, *J* = 7.1 Hz), 5.23 (s, 1 H), 6.89 (d, 2 H, *J* = 2.2 Hz), 7.09–7.28 (m, 6 H), 7.67 (d, 2 H, *J* = 7.3 Hz), 7.96 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 40.9, 61.4, 111.6, 113.7, 119.5, 119.7, 122.2, 123.7, 126.9, 136.6, 173.9.

MS (EI, 70 eV): *m*/*z* (%) = 318 [M^+], 258, 245 (100), 202, 116, 106, 87.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.49; H, 5.68; N, 8.82.

2,2-Di-1*H*-indol-3-ylethanol (8)
A solution of **7** (0.80 g, 2.51 mmol) in anhyd Et_2O (23 mL) was added drop-wise to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (0.22 g, 5.93 mmol) in anhyd Et_2O (18 mL) under a nitrogen atmosphere. The resulting mixture was vigorously stirred at r.t. for 1 h, then quenched by addition of a 10% aq solution of potassium and sodium tartrate (25 mL). The product was extracted with $CHCl_3$ and the combined organic layers were washed with H_2O and brine dried ($MgSO_4$). The solvent was evaporated giving crude alcohol **8** that was used in the next stage of preparation without purification.

Yield: 0.50 g (72%); mp 49–51 °C.

IR (neat): 3404, 3386, 1629 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (br s, 1 H), 4.30 (d, 2 H, *J* = 5.8 Hz), 4.80 (t, 1 H, *J* = 5.8 Hz), 6.98–7.23 (m, 6 H), 7.36 (dd, 2 H, *J* = 8.1, 0.7 Hz), 7.62 (d, 2 H, *J* = 7.7 Hz), 8.04 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 65.3, 110.9, 118.3, 119.8, 120.9, 126.3, 130.4, 138.2.

MS (EI, 70 eV): *m*/*z* (%) = 276 [M^+], 258 (100), 245, 130, 116, 31.

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.20; H, 5.82; N, 10.13.

Streptindole (9)
To a round-bottomed flask and under nitrogen atmosphere were added Ac_2O (0.174 mL, 1.71 mmol), $Mg(ClO_4)_2$ (3.8 mg, 0.0171 mmol), anhyd Et_2O (5 mL) and in three small portions 2,2-di-1*H*-indol-3-ylethanol (**8**) (0.45 g, 1.63 mmol). The mixture was stirred at 20 °C until the reaction was complete (1 h, checked by TLC and GC analyses). After Et_2O and aqueous $NaHCO_3$ had been added, the mixture was stirred for 30 min to decompose the slight excess of Ac_2O. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to give pure streptindole (**9**).

Yield: 0.224 g (98%); uncertain low mp.

IR (neat): 3403, 1722, 1618 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 4.75 (d, 2 H, *J* = 7.0 Hz), 4.97 (t, 1 H, *J* = 7.0 Hz), 6.99–7.27 (m, 6 H), 7.37 (d, 2 H, *J* = 7.7 Hz), 7.64 (d, 2 H, *J* = 7.3 Hz), 8.00 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 33.7, 67.5, 11.3, 116.5, 119.6, 122.2, 122.4, 127.2, 136.6, 171.5.

MS (EI, 70 eV): *m*/*z* (%) = 318 [M^+], 275, 245 (100), 116, 103, 60. 43.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.44; H, 5.66; N, 8.78.

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