

Synthesis of (*R*)- and (*S*)-1-Formyl-6,7,8,9-tetrahydro-*N,N*-dipropyl)-3*H*-benz[*e*]indol-8-amines:  
Potent and Orally Active 5-HT<sub>1A</sub> Receptor Agonists

Chiu-Hong Lin,<sup>\*,†</sup> Michael D. Ennis,<sup>†</sup> Robert L. Hoffman,<sup>†</sup> Gillian Phillips,<sup>†</sup>  
Susanne R. Haadsma-Svensson,<sup>†</sup> Nabil B. Ghazal,<sup>†</sup> and Connie G. Chidester<sup>‡</sup>

Medicinal Chemistry Research and Physical and Analytical Chemistry, Upjohn Laboratories,  
The Upjohn Company, Kalamazoo, Michigan 49001

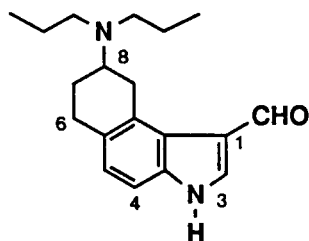
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An efficient synthesis of the potent and orally active 5-HT<sub>1A</sub> agonists, (*R*)-(+)- and (*S*)-(-)-1-formyl-6,7,8,9-tetrahydro-*N,N*-dipropyl-3*H*-benz[*e*]indol-8-amines **1a** and **1b**, is described. This synthesis was accomplished in twelve steps from commercially available 1,5,6,7-tetrahydro-4*H*-indol-4-one (**5**). The key step involved a regio-controlled Friedel-Crafts acylation of 1-(*p*-toluenesulfonyl)indol-4-acetyl chloride with ethylene to yield a versatile synthon, 3-(*p*-toluenesulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-one (**10**). Subsequent coupling of this ketone with chiral  $\alpha$ -methylbenzylamine under reductive amination conditions yielded a mixture of diastereomers. These diastereomers were efficiently separated by either chromatography or fractional recrystallization of the derived hydrochloride salts. Debenzoylation of the pure diastereomers was followed by alkylation and formylation to yield (*R*)-(+)- and (*S*)-(-)-enantiomers **1a** and **1b** with >99% purity.

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### Introduction.

In 1986, Asselin *et al.* [1] reported the synthesis and pharmacological properties of 6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-amine derivatives. They found that the *N,N*-dimethyl and *N,N*-dipropyl analogs displayed potent, orally active dopaminergic activities. Later, in 1989, Wikström *et al.* [2] resolved and investigated the enantiomers of *N,N*-dimethyl analog and found both enantiomers showed mixed 5-HT<sub>1A</sub>/dopamine (D<sub>2</sub>) receptor agonist activities. Between this pair of enantiomers, (*R*)-(+)-enantiomer was found to be 10 times more potent than the corresponding (*S*)-(-)-enantiomer. Recently, Stjernlöf *et al.* [3] reported the synthesis and biological evaluation of the enantiomers of *N,N*-dipropyl analogs **16a** and **16b** and its corresponding 1-formyl analogs **1a** and **1b**. They found that the introduction of a 1-formyl group in both **16a** and **16b** resulted in shifting the mixed 5-HT<sub>1A</sub>/D<sub>2</sub> agonist activities to a selective 5-HT<sub>1A</sub> agonist activity. Both enantiomers **1a** and **1b** are potent 5-HT<sub>1A</sub> agonist with full intrinsic activity and high oral bioavailability (40-70%).

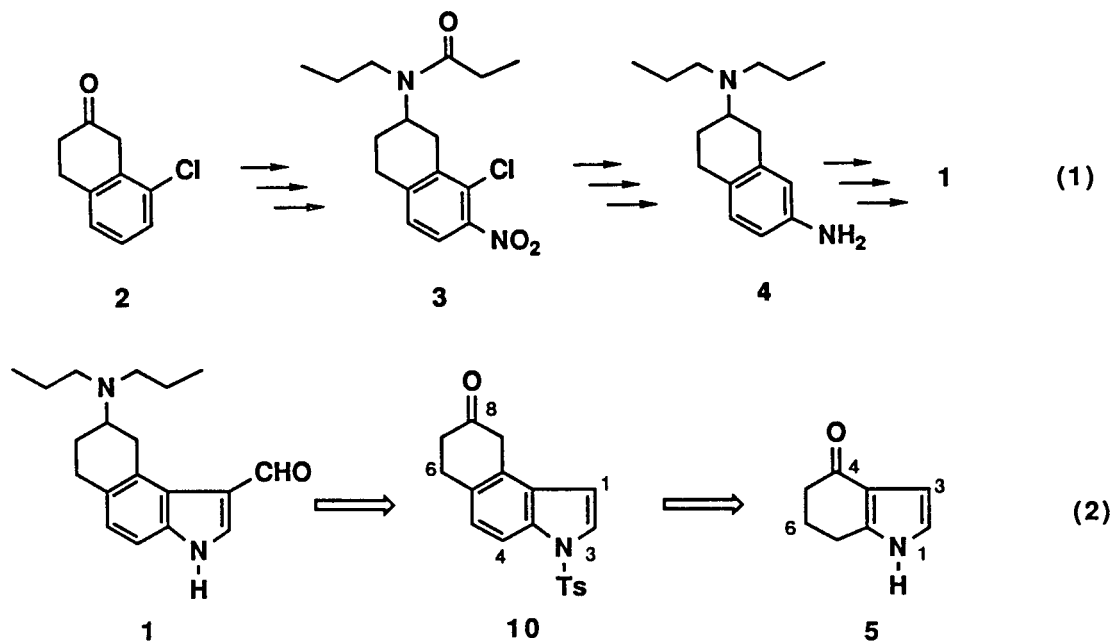


(*8R*)-(+)-**1a**

(*8S*)-(-)-**1b**

The original synthesis was lengthy and required tedious separation of regioisomers [3,4]. As outlined in Equation (1), 8-chloro-2-tetralone was obtained from *o*-chlorophenylacetic acid chloride and ethylene *via* the Friedel-Crafts acylation. Reductive amination with propylamine followed by treatment with propionylchloride/triethylamine in methylene chloride afforded the precursor of **3**. The nitration of this compound resulted in 7-nitro product **3** as well as 5-nitro regioisomer. After a difficult separation of these products, the desired **3** was obtained in 25% yield. A low yield (<20%) was also encountered in the resolution of the racemic intermediate **16ab** (see Scheme 3) with di-*p*-toluoyl-L-tartaric as the resolving agent [3].

To prepare the desired compounds **1a** and **1b** efficiently, we decided to explore an alternative synthesis. As illustrated by the retrosynthetic steps in Equation (2), our strategy involved maintaining the indole carbon fragment intact throughout the synthesis. Thus, the commercially available 1,5,6,7-tetrahydro-4*H*-indol-4-one (**5**) would be an ideal choice as the starting material. We envisioned that transforming **5** to the synthon, 3-(*p*-toluenesulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-one (**10**), would be the key step in achieving our goal. Strategically, the synthon **10** would be a versatile intermediate not only for the synthesis of our targeted molecule **1**, but also for the synthesis of various analogs. The resolution of both enantiomers would be possible by introducing a chiral amine at C-8 in **10**, thus creating a separable diastereomeric pair. We describe herein the efficient synthesis of (*R*)-(+)- and (*S*)-(-)-enantiomers **1a** and **1b**, through the use of the synthon **10**.

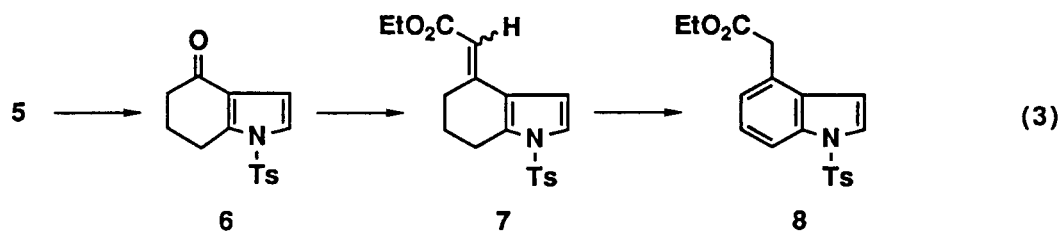


### Results and Discussion.

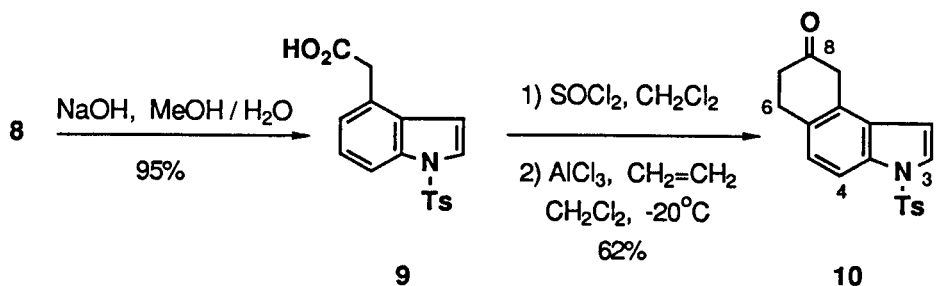
Our original strategy was to establish a large scale process for the synthesis of ketone **10**. We envisioned that **10** might be produced by a Friedel-Crafts methodology similar to that used in the synthesis of 2-tetralone derivatives [5]. The requisite precursor **8** has been described in the literature and was prepared from the commercially-available 1,5,6,7-tetrahydro-4*H*-indol-4-one **5** [6]. As shown in Equation (3), ketone **5** was converted into the *N*-tosyl derivative **6** in 96% yield (NaH/TsCl in THF) [6,7]. The tosylate **6** was then subjected to a Horner-Emmons reaction, with sodium hydride/triethylphosphonoacetate in toluene, to obtain the mixture of *E* and *Z* isomers **7** in 78% yield [6]. Without separating the *E* and *Z* isomers, this mixture was allowed to reflux with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 1,4-dioxane to yield the desired indole-ester **8** in 70% yield [7].

The stage was set for the key step to generate the pivotal synthon **10**. As shown in Scheme 1, hydrolysis of ester **8** with sodium hydroxide in methanol-water provided the acid **9** in almost quantitative yield. This acid was converted into the corresponding acid chloride by reacting with thionyl chloride in methylene chloride. When the acid chloride was subjected to a Friedel-Craft acylation in the presence of aluminum chloride and ethylene in methylene chloride [5], we were able to consistently obtain the synthon **10** from the ester **8** in >60% overall yield.

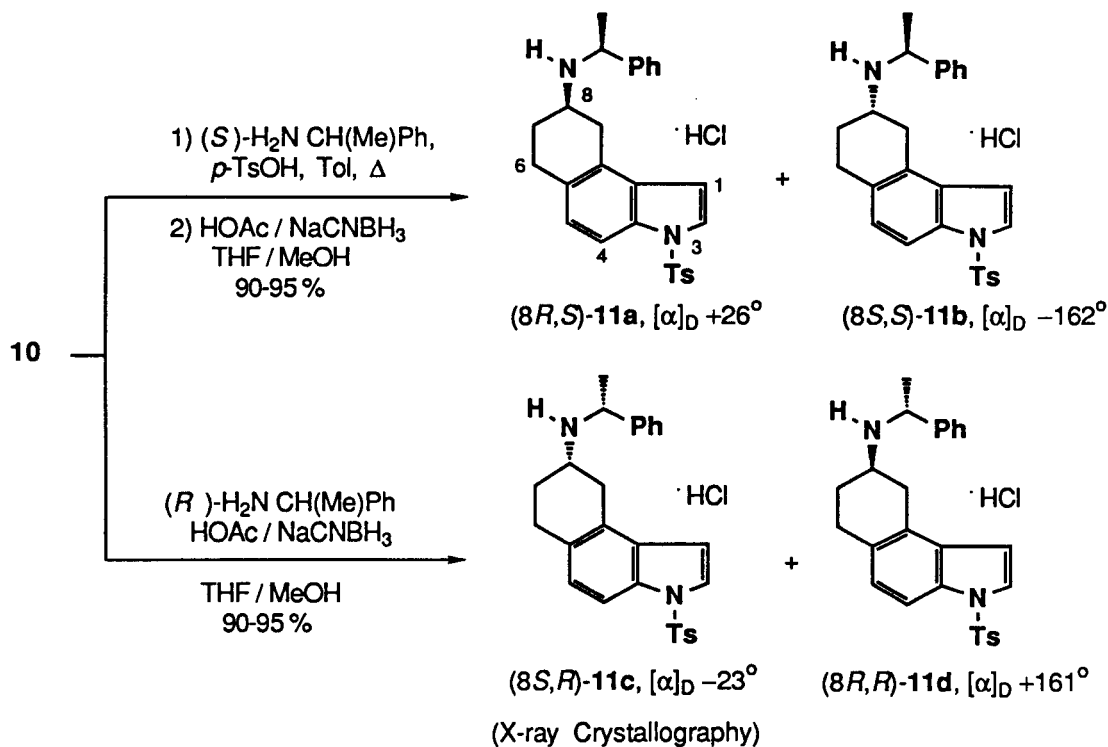
With a large quantity of ketone **10** in hand, we set out to attach the dipropylamino group at C-8 position. A direct reductive amination of this ketone with dipropylamine would have efficiently produced the racemate. However, we expected that the resolution of this racemate would be difficult as demonstrated by Wickström *et al.* [2] in their efforts at resolving the corresponding *N,N*-dimethyl series. We decided therefore to utilize a chiral



## Scheme 1



## Scheme 2



amine to create a pair of potentially separable diastereomers. As shown in Scheme 2, ketone **10** was reacted with 4 equivalents of (*R*)-(+)- $\alpha$ -methylbenzylamine under reductive amination conditions (NaCNBH<sub>3</sub>/HOAc/THF-MeOH) [**8**] to give diastereomers **11c** and **11d** in 45% and 42%, respectively. The diastereomers could be separated by liquid chromatography or fractional recrystallization of the hydrochloride salts. The diastereomer **11c** was determined as (*8S*)-3-*p*-toluenesulfonyl-6,7,8,9-tetrahydro-*N*-(*R*- $\alpha$ -methylbenzyl)-3*H*-benz[e]indol-8-amine hydrochloride by X-ray crystallography (see Figure 1). It is worth commenting upon the relative ease in separating

the diastereomeric pair *via* the fractional recrystallization of the amine hydrochloride salts. We have observed that the diastereomer (*8S,R*)-**11c** is much more readily crystallized than the other diastereomer (*8R,R*)-**11d**. Knowing that between two enantiomers of 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT), a prototype 5-HT<sub>1A</sub> agonist, the (*R*)-enantiomer was more potent than the (*S*)-enantiomer [**9**], we chose to use (*S*)-(-)- $\alpha$ -methylbenzylamine to gain more access to the (*8R*)-enantiomer **11a**. This strategy would provide the diastereomeric pair (*8R,S*)-**11a** and (*8S,S*)-**11b** (Scheme 2), from which we could readily crystallize the desired (*8R,S*)-isomer **11a**. In

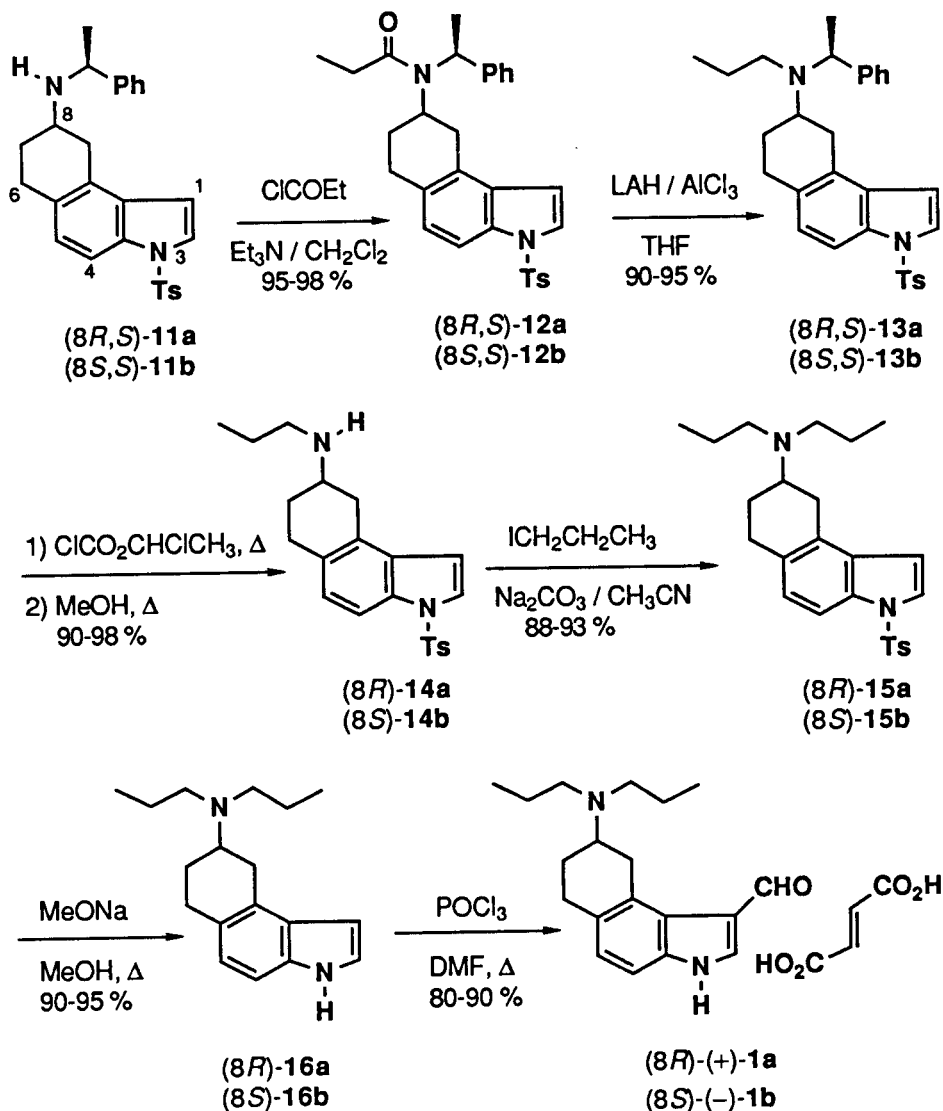
order to conserve the chiral amine, the reductive amination was modified by using only 2 equivalents of amine to initially convert the ketone **10** into the corresponding enamines. The enamines were then reduced with sodium cyanoborohydride to give the desired products **11a** and **11b** in 48% and 43% yield, respectively.

After the absolute configuration of the diastereomers was firmly established, both diastereomers **11a** and **11b** were prepared in large quantity from 40 g of ketone **10a**. As shown in Scheme 3, these diastereomers were treated

95% yield. Unlike **11a/11b**, the diastereomers **12a/12b** were found separable on hplc, allowing for the straightforward determination of diastereomeric excess. In this manner, the chiral purity was found to be better than 99% for each diastereomer (see Experimental section). Treatment of **12a/12b** with a 1:1 mixture of LAH and aluminum chloride [10] in THF afforded the propyl derivatives **13a/13b** in 90-95% yield.

Difficulties were encountered when debenzylation was attempted on **13a/13b** via hydrogenolysis (HCl,

Scheme 3



with propionyl chloride and triethylamine in methylene chloride to yield propionamides **12a/12b** in better than

MeOH/H<sub>2</sub>O, 10% Pd/C). This procedure resulted in the reduction of the indole moiety into the indoline deriva-

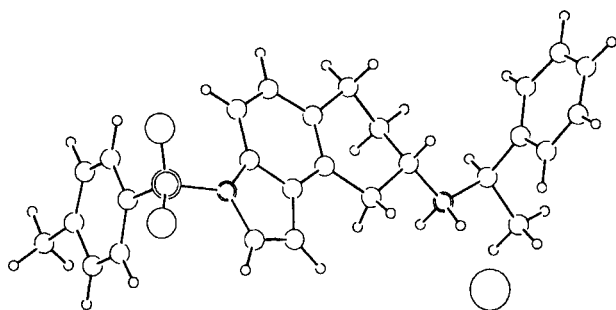


Figure 1. The X-ray crystallographic structure of **11c**, determined as (8*S*)-3-*p*-toluenesulfonyl-6,7,8,9-tetrahydro-*N*-(*R*- $\alpha$ -methylbenzyl)-3*H*-benz[*e*]indol-8-amine hydrochloride.

tives. Successful debenzoylation was realized, however, by employing the chloroformate procedure of Olofson *et al.* [11]. Thus, refluxing a solution of **13a/13b** in 1-chloroethyl chloroformate for 48 hours followed by

Table 1  
Fractional Coordinates ( $\times 10^4$ ) and  $B_{eq}$  or  $B(\text{\AA}^2)$  for **11c**

$$B_{eq} = 4/3(a^2B_{11} + b^2B_{22} + c^2B_{33} + abc\cos\gamma B_{12} + accos\beta B + bccos\alpha B_{23})$$

	x	y	z	$B_{eq} (\text{\AA}^2)$
CL	2426 (1)	10260	5817 (2)	5.0 (1)
N	2880 (3)	6223 (12)	6316 (6)	3.4 (3)
C (1)	3522 (3)	6102 (16)	7503 (7)	3.1 (3)
C (4)	4775 (4)	8584 (15)	7467 (7)	3.1 (3)
C (5)	5374 (4)	8342 (17)	8037 (7)	3.7 (4)
C (6)	5658 (4)	6760 (18)	8620 (9)	5.0 (5)
C (7)	5333 (4)	5464 (19)	8629 (8)	5.0 (4)
C (8)	4726 (4)	5639 (15)	8073 (7)	3.6 (4)
C (9)	4402 (4)	4135 (16)	8197 (9)	4.8 (4)
C (10)	3747 (4)	4163 (17)	7255 (9)	4.5 (4)
N (11)	5584 (3)	9951 (14)	7903 (6)	4.1 (3)
C (12)	5116 (4)	11143 (17)	7233 (7)	4.2 (4)
C (13)	4630 (4)	10383 (19)	6971 (7)	3.9 (3)
C (14)	2502 (4)	5007 (16)	6447 (8)	4.5 (4)
C (15)	1868 (4)	5433 (20)	5516 (8)	5.4 (4)
C (16P)	2636 (4)	5209 (24)	7483 (7)	4.4 (4)
C (17P)	2597 (5)	6937 (20)	7787 (9)	5.2 (5)
C (18P)	2690 (5)	7089 (23)	8697 (10)	6.4 (6)
C (19P)	2790 (5)	5604 (35)	9268 (10)	8.3 (7)
C (20P)	2843 (6)	3951 (31)	8979 (11)	9.1 (8)
C (21P)	2762 (5)	3657 (20)	8065 (10)	5.9 (5)
S	6216 (1)	10143 (7)	8123 (2)	5.0 (1)
O (S1)	6645 (3)	9341 (13)	9120 (5)	5.6 (3)
O (S2)	6256 (3)	12053 (13)	7933 (6)	6.2 (3)
C (22P)	6141 (4)	8703 (19)	7221 (8)	4.7 (4)
C (23P)	6345 (6)	6948 (23)	7512 (9)	6.5 (6)
C (24P)	6248 (6)	5898 (28)	6813 (12)	9.8 (9)
C (25P)	5947 (6)	6310 (22)	5793 (14)	8.1 (7)
C (25M)	5786 (7)	5086 (33)	4860 (15)	11.0 (9)
C (26P)	5729 (5)	8143 (26)	5484 (10)	6.7 (6)
C (27P)	5836 (5)	9360 (19)	6229 (10)	5.8 (5)
C (1EA)	5000	10283 (29)	10000	6.2 (3)
C (2EA)	4504 (7)	9497 (28)	9680 (13)	4.2 (3)
C (3EA)	4057 (7)	10543 (32)	9440 (13)	4.9 (4)
C (4EA)	4409 (10)	8147 (38)	9418 (18)	6.7 (5)

Table 1a  
Fractional Coordinates ( $\times 10^3$ ) and Isotropic Temperature Factors for Hydrogen Atoms for **11c**

	x	y	z	$B (\text{\AA}^2)$
H (1)	361	647	782	3.4
H (NA)	276	753	626	2.8
H (NB)	280	584	566	2.8
H (3A)	360	730	613	3.4
H (3B)	371	875	699	3.4
H (7)	608	659	901	4.6
H (8)	552	432	904	4.6
H (9A)	444	437	883	3.9
H (10A)	369	383	661	5.9
H (11B)	353	325	736	4.6
H (12A)	456	289	824	3.5
H (13)	514	1237	698	4.1
H (14)	423	1094	651	3.5
H (15)	257	369	638	3.8
H (15A)	181	526	486	5.7
H (15B)	160	456	551	5.7
H (15C)	177	673	555	5.7
H (17P)	250	804	735	4.8
H (18P)	267	834	893	5.7
H (19P)	282	573	990	5.9
H (20P)	294	286	943	6.1
H (21P)	278	240	784	5.9
H (23P)	656	651	824	5.8
H (24P)	640	461	703	5.2
H (26P)	550	854	475	5.8
H (27P)	569	1067	605	5.2
H (25A)	594	381	510	6.5
H (25B)	595	566	455	6.5
H (25C)	535	502	433	6.5

methanolysis afforded the desired secondary amines **14a/14b** in excellent yield (90-98%). Heating **14a/14b** with iodopropane and sodium carbonate in acetonitrile gave the dipropyl derivatives **15a/15b** in 88-93% yield. The removal of the tosyl group was performed by heating **15a/15b** in sodium methoxide/methanol to give indole derivatives **16a/16b** in 90-95% yield. In the final step, the indole derivatives **16a/16b** were then converted into the formyl derivatives **1a/1b** via the Vilsmeier-Haack reaction ( $\text{POCl}_3/\text{DMF}$ ) in 80-90% yield. The physical data including the optical rotations of **1a** ( $+112.5^\circ$ , lit  $+112^\circ$ ) and **1b** ( $-113.3^\circ$ , lit  $-112^\circ$ ) were in agreement with those reported by Stjernlöf *et al.* [3].

#### Conclusion.

We have described herein an efficient synthesis of (*R*)-(+)- and (*S*)-(-)-1-formyl-6,7,8,9-tetrahydro-*N,N*-(di-*n*-propyl)-3*H*-benz[*e*]indol-8-amines, **1a** and **1b**. Both enantiomers were prepared in >99% purity. The separation of these enantiomers was achieved by coupling a chiral auxiliary, (*S*)-(-)- $\alpha$ -methylbenzylamine, to the ketone **10** to generate diastereomers, (8*R,S*)-**11a** and (8*S,S*)-**11b**, under reductive amination conditions. These diastereomers were then separated (>40% for each diastereomer)

by either chromatography or fractional recrystallization of the hydrochloride salts. Pivotal to this synthesis was preparation of the key synthon **10** in a five step sequence from readily available 1,5,6,7-tetrahydro-4*H*-indol-4-one

**1**. The synthon **10** can be easily prepared in a large scale process and well-suited for elaboration to various analogs. The biological evaluation of both enantiomers **1a** and **1b** was already described by Stjernlöf *et al.* [3,4].

Table 2  
Bond lengths (Å), angles (°), and torsion angles (°) for **11c**

N-C(1)	1.501(9)	C(16P)-C(17P)	1.378(21)
N-C(14)	1.537(9)	C(16P)-C(21P)	1.373(21)
C(1)-C(2)	1.526(12)	C(17P)-C(18P)	1.364(16)
C(1)-C(10)	1.517(16)	C(18P)-C(19P)	1.338(26)
C(2)-C(3)	1.537(9)	C(19P)-C(20P)	1.333(31)
C(3)-C(4)	1.387(12)	C(20P)-C(21P)	1.399(17)
C(3)-C(8)	1.389(15)	S-O(S1)	1.439(8)
C(4)-C(5)	1.401(9)	S-O(S2)	1.437(11)
C(4)-C(13)	1.454(17)	S-C(22P)	1.723(12)
C(5)-C(6)	1.393(17)	C(22P)-C(23P)	1.357(21)
C(5)-N(11)	1.399(14)	C(22P)-C(27P)	1.381(17)
C(6)-C(7)	1.346(14)	C(23P)-C(24P)	1.263(21)
C(7)-C(8)	1.417(9)	C(24P)-C(25P)	1.370(24)
C(8)-C(9)	1.544(12)	C(25P)-C(25M)	1.580(26)
C(9)-C(10)	1.555(13)	C(25P)-C(26P)	1.422(24)
N(11)-C(12)	1.406(13)	C(26P)-C(27P)	1.386(20)
N(11)-S	1.665(3)	C(1EA)-C(2EA)	1.333(15)
C(12)-C(13)	1.329(10)	C(2EA)-C(3EA)	1.344(20)
C(14)-C(15)	1.544(13)	C(2EA)-C(4EA)	1.034(34)
C(14)-C(16P)	1.514(13)		
C(1)-N-C(14)	115.8(7)	C(15)-C(14)-C(16P)	114.7(5)
N-C(1)-C(2)	105.7(8)	C(14)-C(16P)-C(17P)	118.7(12)
N-C(1)-C(10)	111.4(8)	C(14)-C(16P)-C(21P)	119.1(13)
C(2)-C(1)-C(10)	110.5(5)	C(17P)-C(16P)-C(21P)	122.0(9)
C(1)-C(2)-C(3)	113.7(8)	C(16P)-C(17P)-C(18P)	118.3(13)
C(2)-C(3)-C(4)	120.1(9)	C(17P)-C(18P)-C(19P)	121.7(15)
C(2)-C(3)-C(8)	120.5(7)	C(18P)-C(19P)-C(20P)	119.2(12)
C(4)-C(3)-C(8)	119.4(6)	C(19P)-C(20P)-C(21P)	123.2(17)
C(3)-C(4)-C(5)	119.4(9)	C(16P)-C(21P)-C(20P)	115.4(14)
C(3)-C(4)-C(13)	133.2(6)	N(11)-S-O(S1)	106.3(3)
C(5)-C(4)-C(13)	107.3(7)	N(11)-S-O(S2)	105.3(4)
C(4)-C(5)-C(6)	122.2(8)	N(11)-S-C(22P)	103.8(4)
C(4)-C(5)-N(11)	106.6(9)	O(S1)-S-O(S2)	120.4(5)
C(6)-C(5)-N(11)	131.2(6)	O(S1)-S-C(22P)	107.7(6)
C(5)-C(6)-C(7)	117.0(7)	O(S2)-S-C(22P)	111.9(5)
C(6)-C(7)-C(8)	123.2(11)	S-C(22P)-C(23P)	117.7(9)
C(3)-C(8)-C(7)	118.7(8)	S-C(22P)-C(27P)	117.8(10)
C(3)-C(8)-C(9)	122.1(6)	C(23P)-C(22P)-C(27P)	124.2(11)
C(7)-C(8)-C(9)	119.0(9)	C(22P)-C(23P)-C(24P)	115.9(13)
C(8)-C(9)-C(10)	109.9(9)	C(23P)-C(24P)-C(25P)	127.5(18)
C(1)-C(10)-C(9)	107.7(9)	C(24P)-C(25P)-C(25M)	131.3(16)
C(5)-N(11)-C(12)	108.7(6)	C(24P)-C(25P)-C(26P)	116.7(15)
C(5)-N(11)-S	125.5(7)	C(25M)-C(25P)-C(26P)	112.0(15)
C(12)-N(11)-S	122.4(6)	C(25P)-C(26P)-C(27P)	118.0(13)
N(11)-C(12)-C(13)	109.5(10)	C(22P)-C(27P)-C(26P)	117.7(13)
C(4)-C(13)-C(12)	107.9(8)	C(1EA)-C(2EA)-C(3EA)	120.5(19)
N-C(14)-C(15)	106.0(8)	C(1EA)-C(2EA)-C(4EA)	120.7(14)
N-C(14)-C(16P)	113.9(9)	C(3EA)-C(2EA)-C(4EA)	116.7(16)

Table 2 (Continued)  
Bond lengths (Å), angles (°), and torsion angles (°) for 11c

C(14)-N-C(1)-C(2)	-177.8(7)	S-N(II)-C(12)-C(13)	162.1(7)
C(14)-N-C(1)-C(10)	62.1(9)	C(5)-N(II)-S-O(S1)	-48.2(9)
C(1)-N-C(14)-C(15)	177.7(8)	C(5)-N(II)-S-O(S2)	-177.0(8)
C(1)-N-C(14)-C(16P)	50.6(11)	C(5)-N(II)-S-C(22P)	65.3(9)
N-C(1)-C(2)-C(3)	-166.2(8)	C(12)-N(II)-S-O(S1)	155.0(8)
C(10)-C(1)-C(2)-C(3)	-45.5(11)	C(12)-N(II)-S-O(S2)	26.2(9)
N-C(1)-C(10)-C(9)	-175.8(6)	C(12)-N(II)-S-C(22P)	-91.5(10)
C(2)-C(1)-C(10)-C(9)	67.0(9)	N(II)-C(12)-C(13)-C(4)	-1.4(11)
C(1)-C(2)-C(3)-C(4)	-168.0(8)	N-C(14)-C(16P)-C(17P)	57.6(8)
C(1)-C(2)-C(3)-C(8)	15.0(12)	N-C(14)-C(16P)-C(21P)	-125.9(8)
C(2)-C(3)-C(4)-C(5)	-179.6(8)	C(15)-C(14)-C(16P)-C(17P)	-64.8(11)
C(2)-C(3)-C(4)-C(13)	4.1(15)	C(15)-C(14)-C(16P)-C(21P)	111.7(10)
C(8)-C(3)-C(4)-C(5)	-2.5(13)	C(14)-C(16P)-C(17P)-C(18P)	176.7(6)
C(8)-C(3)-C(4)-C(13)	-178.8(9)	C(21P)-C(16P)-C(17P)-C(18P)	0.3(11)
C(2)-C(3)-C(8)-C(7)	179.2(8)	C(14)-C(16P)-C(21P)-C(20P)	-176.0(7)
C(2)-C(3)-C(8)-C(9)	-6.5(13)	C(17P)-C(16P)-C(21P)-C(20P)	0.4(11)
C(4)-C(3)-C(8)-C(7)	2.1(13)	C(16P)-C(17P)-C(18P)-C(19P)	-3.1(12)
C(4)-C(3)-C(8)-C(9)	176.4(9)	C(17P)-C(18P)-C(19P)-C(20P)	5.0(13)
C(3)-C(4)-C(5)-C(6)	2.0(14)	C(18P)-C(19P)-C(20P)-C(21P)	-4.2(15)
C(3)-C(4)-C(5)-N(11)	-176.4(8)	C(19P)-C(20P)-C(21P)-C(16P)	1.5(13)
C(13)-C(4)-C(5)-C(6)	179.2(9)	N(II)-S-C(22P)-C(23P)	-95.0(7)
C(13)-C(4)-C(5)-N(II)	0.9(10)	N(II)-S-C(22P)-C(27P)	79.6(7)
C(3)-C(4)-C(13)-C(12)	177.0(10)	O(S1)-S-C(22P)-C(23P)	17.4(7)
C(5)-C(4)-C(13)-C(12)	0.3(11)	O(S1)-S-C(22P)-C(27P)	-168.0(6)
C(4)-C(5)-C(6)-C(7)	-1.1(15)	O(S2)-S-C(22P)-C(23P)	151.9(6)
N(II)-C(5)-C(6)-C(7)	176.9(10)	O(S2)-S-C(22P)-C(27P)	-33.5(7)
C(4)-C(5)-N(II)-C(12)	-1.7(10)	S-C(22P)-C(23P)-C(24P)	175.5(7)
C(4)-C(5)-N(II)-S	-161.1(7)	C(27P)-C(22P)-C(23P)-C(24P)	1.3(12)
C(6)-C(5)-N(II)-C(12)	-179.8(12)	S-C(22P)-C(27P)-C(26P)	-174.1(5)
C(6)-C(5)-N(II)-S	20.7(15)	C(23P)-C(22P)-C(27P)-C(26P)	0.1(11)
C(5)-C(6)-C(7)-C(8)	0.6(16)	C(22P)-C(23P)-C(24P)-C(25P)	-2.2(14)
C(6)-C(7)-C(8)-C(3)	-1.2(15)	C(23P)-C(24P)-C(25P)-C(25M)	-177.6(9)
C(6)-C(7)-C(8)-C(9)	-175.7(10)	C(23P)-C(24P)-C(25P)-C(26P)	1.7(13)
C(3)-C(8)-C(9)-C(10)	27.3(12)	C(24P)-C(25P)-C(26P)-C(27P)	-0.1(13)
C(7)-C(8)-C(9)-C(10)	-158.4(9)	C(25M)-C(25P)-C(26P)-C(27P)	179.4(7)
C(8)-C(9)-C(10)-C(1)	-56.1(8)	C(25P)-C(26P)-C(27P)-C(22P)	-0.7(10)
C(5)-N(II)-C(12)-C(13)	1.9(11)		

Table 3

Close Intermolecular Contacts and Intramolecular Ethyl Acetate Distances Between Non-hydrogen Atoms for 11c.

Related atom.....Atom	Symmetry	Distance (Å)
O(S2).....C(24P)	x, y-1, z	3.336(20)
CL.....N	1/2-x, y-1/2, 1-z	3.144 (7)
O(S1).....C(19P)	x-1/2, y-1/2, z	3.352(9)
C(7).....C(4EA)	1-x, y, 2-z	3.435(26)
C(18P).....O(S1)	1-x, y, 2-z	3.287 (16)
C(19P).....O(S1)	1-x, y, 2-z	3.419 (23)
C(1EA).....C(2EA)	1-x, y, 2-z	1.333 (15)
C(1EA).....C(4EA)	1-x, y, 2-z	2.062(28)
C(2EA).....C(4EA)	1-x, y, 2-z	2.736 (21)
C(4EA).....C(4EA)	1-x, y, 2-z	2.734 (16)

Table 4

Hydrogen bonds for 11c. D Represents Donor, A Acceptor; Distances are in Å and Angles are in °. Standard Deviations are in Parentheses.

D	A	A AT	D...A	H...A	<D-H...A
N	CL	x, y, z	3.100(9)	2.12	167
N	CL	1/2-x, y-1/2, 1-z	3.144 (7)	2.15	174

## EXPERIMENTAL

Analytical tlc was performed on Analtech 10 x 20 cm (250 microns) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. The <sup>1</sup>H nmr spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in carbon tetrachloride solution unless noted otherwise. Chemical shifts (δ) were reported in parts per million relative to tetramethylsilane as internal standard. Flash column chromatography and medium pressure liquid chromatography were performed with 400 g to 1 kg silica gel 60 (230-400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. Methylene chloride, methanol, tetrahydrofuran, ethyl acetate and hexane hplc gradewere used. All reactions were performed under a nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine based products were converted into the hydrochloride salts by dissolving the free base in methanolic hydrogen chloride solu-

tion [12]. The solvent was removed and the resulting residue was evaporated with toluene *in vacuo*, followed by recrystallization from an appropriate solvent. Other physical data, such as ir (infrared spectra), ms (mass spectra), elemental analyses, and optical rotations were performed by the Physical and Analytical Chemistry Unit of the Upjohn Laboratories. The elementary analyses were within  $\pm 0.4\%$  of the calculated values.

#### 1-(*p*-Toluenesulfonyl)indol-4-acetic Acid (**9**).

A solution of ester **8** (25.7 g, 72.0 mmoles) in methanol (192 ml) was treated with 3*N* sodium hydroxide (48 ml) at room temperature. The milky suspension was stirred for 2 hours and it became a clear solution. The mixture was then neutralized with 6*N* hydrochloric acid to pH 6-7 and methanol was removed *in vacuo*. The concentrate was extracted with warm ethyl acetate. The organic layer was washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The solid was recrystallized from hexane/ethyl acetate to yield 22.6 g (95%) of the desired acid **9**: mp 150-151°; <sup>1</sup>H nmr:  $\delta$  7.91 (d, *J* = 8.4 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 3.5 Hz, 1 H), 7.33-7.10 (m, 4 H), 6.68 (d, *J* = 3.5 Hz, 1 H), 3.78 (s, 2 H), 2.32 (s, 3 H); ir (mull):  $\nu$  max 1690 and 1595 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>17</sub>H<sub>15</sub>NSO<sub>4</sub>: C, 61.99; H, 4.59; N, 4.25. Found: C, 61.78; H, 4.67; N, 4.17.

#### 3-(*p*-Toluenesulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-one (**10**).

A solution of acid **9** (19.9 g, 60 mmoles) in 40 ml of methylene chloride was treated with thionyl chloride (8.7 ml, 120 mmoles) at room temperature. The resulting black colored mixture was stirred at room temperature for 2 hours. The reagent and the solvent was removed *in vacuo* while adding heptane to facilitate the removal of the excess thionyl chloride. The resulting black oil was dissolved methylene chloride (100 ml) and ready for the next step. In a three-neck, round-bottomed flask equipped with a magnetic stirring bar, a dropping funnel, and a gas inlet attached to a 16 gauge long syringe needle, was charged with aluminum chloride (32 g, 240 mmoles) and methylene chloride (500 ml). The solution was cooled to -20° and ethylene gas was bubbled *via* a syringe. After 10 minutes, the acid chloride in methylene chloride prepared above was added slowly over a period of 30 minutes *via* a dropping funnel. The bubbling of the ethylene gas was continued for 1 hour at -20°. The reaction mixture was then poured into an Erlenmeyer flask containing ice/water (200 ml) and extracted with methylene chloride (2 x 1 l). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on 1 kg of silica gel, eluting with methylene chloride/hexane (9:1), and collecting 300 ml fractions. Fractions homogeneous by tlc were combined and concentrated *in vacuo* to give a brown solid (13.0 g). Recrystallization from ethyl acetate afforded an off-white solid. The mother liquor was concentrated and chromatographed to yield additional 5.7 g of an off-white solid. Combining both solids yielded 12.7 g (62%) of the desired ketone **10**, mp 193-194°; <sup>1</sup>H nmr:  $\delta$  7.83 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 3.5 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 6.59 (d, *J* = 3.5 Hz, 1 H), 3.69 (s, 2 H), 3.14 (t, *J* = 7.0 Hz, 2 H), 2.61 (t, *J* = 7.0 Hz, 2 H), 2.34 (s, 3 H); ir (mull):  $\nu$  max 1710 and 1596

cm<sup>-1</sup>; ms: M<sup>+</sup> 339, other ions at m/z 297, 184, 155, 142, 191.

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>NSO<sub>3</sub>: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.18; H, 5.04; N, 4.02.

#### (8*R*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*-[(*S*)-methylbenzyl]-3*H*-benz[*e*]indol-8-amine Hydrochloride (**11a**) and Its (8*S*,*S*)-Diastereomer (**11b**).

A solution of ketone **10** (10.2 g, 30.0 mmoles), (*S*)-(-)- $\alpha$ -methylbenzylamine (7.7 ml, 60.0 mmoles), and *p*-toluenesulfonic acid monohydrate (0.1 g) in 300 ml toluene was refluxed in a flask attached with Dean-Stark trap. After 18 hours, the solvent was removed *in vacuo* to give a deep brown oil. The oil was then dissolved in 150 ml THF/methanol (1:1) and cooled to 0-5°. The brown solution was treated with acetic acid (9.0 ml) until pH 4-5, stirred for 30 minutes, and treated with sodium cyanoborohydride (3.8 g, 60 mmoles). The resulting mixture was stirred at room temperature for 18 hours. The reaction was quenched with 10% sodium hydroxide until pH >13 and THF/methanol was removed *in vacuo*. The residue was diluted with water (200 ml), brine, dried (magnesium sulfate), and concentrated *in vacuo* to give a dark, greenish-brown oil. The oil was purified by liquid chromatography on 1.2 kg of silica gel, eluting with hexane/acetone (2:1), and collecting 40 ml fractions (Note). Fractions 89-120 yielded a dark brown oil which was repurified on 800 g of silica gel, using the same conditions, to give a greenish oil (8.45 g). This oil was converted into the hydrochloride salt and recrystallized from ethyl acetate/methanol to yield the diastereomer **11a** as a white solid (6.9 g, 48%) (Note). Fractions 121-188 yielded a greenish brown oil which was repurified by liquid chromatography as above to give a greenish oil (7.2 g). This oil was converted into the hydrochloride salt and recrystallized from ether/2-propanol to give the other diastereomer **11b** as a white solid (6.2 g, 43%).

Compound **11a** had mp 272-273°; <sup>1</sup>H nmr:  $\delta$  7.77-7.42 (m, 9 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 3.5 Hz, 1 H), 4.72 (q, *J* = 7.0 Hz, 1 H), 3.50-1.74 (m, 7 H), 2.32 (s, 3 H), 1.71 (d, *J* = 7.0 Hz, 3 H) (contained about 5% of ethyl acetate although the solid was heated at 100° in the vacuum oven overnight); ir (mull):  $\nu$  max 1740 (from ethyl acetate), 1607, 1595, and 1587 cm<sup>-1</sup>; ms: M<sup>+</sup> 444, other ions at m/z 429, 339, 322, 184, 168, 142, 105; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +26° (c 0.4, methanol).

*Anal.* Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S•HCl•0.44EtOAc: C, 66.45; H, 6.31; N, 5.39. Found: C, 66.44; H, 6.31; N, 5.32.

Compound **11b** had mp 246-247°; <sup>1</sup>H nmr:  $\delta$  7.77-7.45 (m, 9 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.80 (d, *J* = 3.5 Hz, 1 H), 4.75 (q, *J* = 7.0 Hz, 1 H), 3.50-1.74 (m, 7 H), 2.32 (s, 3 H), 1.71 (d, *J* = 7.0 Hz, 3 H); ir (mull):  $\nu$  max 1606, 1592, and 1583 cm<sup>-1</sup>; ms: M<sup>+</sup> 444, other ions at m/z 429, 339, 322, 184, 168, 142, 105; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -162° (c 0.46, methanol).

*Anal.* Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S•HCl: C, 67.41; H, 6.08; N, 5.83. Found: C, 67.33; H, 6.07; N, 5.68. *Note:* The separation of the diastereomers can also be achieved by the fractional recrystallization of the mixture of the hydrochloride salts. The less polar diastereomeric salt **11a** can be easily recrystallized from ethyl acetate/methanol whereas the more polar salt **11b** can be recrystallized from ether/2-propanol.

#### (8*S*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*-[(*R*)- $\alpha$ -methylbenzyl]-3*H*-benz[*e*]indol-8-amine Hydrochloride (**11c**) and Its (8*R*,*R*)-Diastereomer (**11d**).



A solution of ketone **10** (1.36 g, 4.0 mmoles), (*R*)-(-)- $\alpha$ -methylbenzylamine (2.0 ml, 16 mmol), and acetic acid (0.12 ml) in THF/methanol (60 ml) was cooled to 0-5°. After 1 hour, the solution was treated with sodium cyanoborohydride (0.5 g, 8.0 mmole) and stirred at room temperature for 18 hours. The reaction was quenched with saturated sodium bicarbonate, concentrated, and extracted with methylene chloride (2 x 600 ml). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 600 g of silica gel, eluting with hexane/acetone (4:1), and collecting 40 ml fractions. Fractions 64-95 gave an oil which was converted into the hydrochloride salt and recrystallized from ethyl acetate/methanol to give the diastereomer **11c** as a white solid (0.8 g, 45%). Fractions 101-127 afforded an oil which was converted into the hydrochloride salt and recrystallized from ethyl acetate/hexane to give the other diastereomer **11d** as a white solid (0.75 g, 42%).

Compound **11c** had mp 271-272°; <sup>1</sup>H nmr and ir, identical to those of **11a**; ms: Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S 444.1871. Found: 444.1870; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -23° (c 0.98, methanol).

Anal. Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S•HCl•0.27 EtOAc: C, 66.80; H, 6.22; N, 5.55. Found: C, 66.80; H, 6.26; N, 5.57. X-ray chromatography was carried out on this compound and confirmed its absolute configuration, see Figure 1.

Compound **11d** had mp 241-242°; <sup>1</sup>H nmr and ir, identical to those of **11b**; ms: Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S: 444.1871. Found: 444.1878; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +161° (c 0.28, methanol).

Anal. Calcd. for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S•HCl: C, 67.41; H, 6.08; N, 5.83. Found: C, 67.14; H, 6.09; N, 5.76.

(*8R*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*-propionyl-*N*-[(*S*)- $\alpha$ -methylbenzyl]-3*H*-benz[e]indol-8-amine (**12a**) and Its (*8S,S*)-Diastereomer (**12b**).

A solution of **11a** (6.9 g, 94% pure, 13.6 mmoles) and triethylamine (5.7 ml, 40.8 mmoles) in methylene chloride (136 ml) was treated with propionyl chloride (1.8 ml, 20.4 mmoles) at room temperature and stirred for 3 hours. The reaction was quenched with methanol (5 ml), stirred for 1 hour and treated with 10% sodium hydroxide until pH >13. The mixture was then extracted with methylene chloride (2 x 1 l) and the combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 800 g silica gel, eluting with hexane/ethyl acetate (1:1), and collecting 40 ml fractions. Fractions homogeneous by tlc were combined and concentrated *in vacuo* to give pure **12a** as a white solid (6.7 g, 99%): mp 100-102°; <sup>1</sup>H nmr:  $\delta$  7.80-7.64 (m, 3H), 7.50 (broad d, *J* = 3.5 Hz, 1 H), 7.38-6.88 (m, 8 H), 6.59 (d, *J* = 3.5 Hz, 1 H), 5.22-5.12 and 3.92-3.72 (m, 1 H), 2.88-1.10 (m, 8 H), 2.33 (s, 3 H), 1.68 (d, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H); ir (mull):  $\nu$  max 1640, 1597, and 1520 cm<sup>-1</sup>; ms: no M<sup>+</sup> ions at *m/z* 323, 169, 105.

Anal. Calcd. for C<sub>30</sub>H<sub>33</sub>N<sub>2</sub>O<sub>3</sub>S: C, 71.97; H, 6.44; N, 5.60. Found: C, 71.80; H, 6.67; N, 5.40.

The other diastereomer was prepared from **11b** (5.5 g, 11.5 mmoles), using the same procedure as above, to yield pure **12b** as a white solid (5.65 g, 98%): mp 94-96°; <sup>1</sup>H nmr:  $\delta$  7.28-7.62 (m, 3 H), 7.40 (broad d, *J* = 3.5 Hz, 1 H), 7.35-6.90 (m, 8 H), 6.83 (broad d, *J* = 3.5 Hz, 1 H), 5.20-5.10 and 3.70-3.52 (m, 1

H), 3.52-1.12 (m, 8 H), 2.32 (s, 3 H), 1.68 (d, *J* = 7.0 Hz, 3 H), 1.94 (t, *J* = 7.0 Hz, 3 H); ms: no M<sup>+</sup> ions at *m/z* 323, 169, 105.

Anal. Calcd. for C<sub>30</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>S: C, 71.97; H, 6.44; N, 5.60. Found: C, 71.81; H, 6.55; N, 5.40.

Analysis (hplc) of diastereomers **12a** and **12b** was accomplished as follows: column, Beckman Ultrasphere RP Column (10 mm x 25 cm); eluant, 30% pH 3 phosphate buffer/acetonitrile, flow rate, 5 ml/minute; retention times, **12a** 14.32 minutes, **12b** 16.14 minutes.

(*8R*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*-propyl-*N*-[(*S*)- $\alpha$ -methylbenzyl]-3*H*-benz[e]indol-8-amine (**13a**) and Its (*8S,S*)-Diastereomer (**13b**).

A suspension of LAH (1.5 g, 39.6 mmoles) in THF (200 ml) was cooled to 0-5° and aluminum chloride (5.3 g, 39.6 mmoles) powder was added slowly *via* a powder funnel. After stirring the mixture for 10 minutes, the starting material **12a** (6.6 g, 13.2 mmoles in THF (60 ml) was added slowly over 30 minutes. The mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with 20% sodium hydroxide (30 ml), then diluted with water, and extracted with methylene chloride (2 x 1 l). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 800 g of silica gel, eluting with hexane/ethyl acetate (4:1), and collecting 40 ml fractions. Fractions homogeneous by tlc were combined and concentrated *in vacuo* to yield pure **13a** as a colorless oil (6.42 g, 97%): <sup>1</sup>H nmr:  $\delta$  7.75-7.64 (m, 3 H), 7.51 (d, *J* = 3.5 Hz, 1H), 7.38-6.94 (m, 8 H), 6.64 (d, *J* = 3.5 Hz, 1 H), 4.04 (q, *J* = 7.0 Hz, 1 H), 3.12-1.42 (m, 11H), 2.32 (s, 3 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 0.83 (t, *J* = 7.0 Hz, 3 H); ir (mull):  $\nu$  max 1598, and 1589 cm<sup>-1</sup>; ms: M<sup>+</sup> 486, other ions at *m/z* 471, 457, 381, 353, 324, 188, 105.

Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>S: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.08; H, 7.32; N, 5.60.

The other diastereomer was prepared from **12b** (5.6 g, 11.2 mmoles), using the same procedure as above, to yield pure **13b** as a colorless oil (5.04 g, 93%): <sup>1</sup>H nmr:  $\delta$  7.74-7.62 (m, 3 H), 7.49 (d, *J* = 3.5 Hz, 1H), 7.30-6.90 (m, 8 H), 6.57 (d, *J* = 3.5 Hz, 1 H), 4.08 (q, *J* = 7.0 Hz, 1 H), 3.52-1.12 (m, 11 H), 2.32 (s, 3 H), 1.68 (d, *J* = 7.0 Hz, 3 H), 1.94 (t, *J* = 7.0 Hz, 3 H); ms: no M<sup>+</sup> ions at *m/z* 323, 169, 105.

Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>S: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.18; H, 7.31; N, 5.63.

(*R*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N*-propyl-3*H*-benz[e]indol-8-amine Hydrochloride (**14a**) and Its (*S*)-Enantiomer (**14b**).

A solution of **13a** (4.14 g, 8.5 mmoles) in 1-chloro-ethylchloroformate (8.5 ml, 85 mmoles) was refluxed (bath temperature 130° for 24 hours. The bath temperature was then lowered to 80° and treated with methanol (40 ml) and refluxed for 1 hour. Methanol was removed *in vacuo* and the concentrate was recrystallized from ethyl acetate/methanol to yield **14a** as an off-white solid (3.45 g, 98%): mp 273-274°; <sup>1</sup>H nmr:  $\delta$  7.78 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 3.5 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 3.5 Hz, 1 H), 3.60-1.52 (m, 11 H), 2.33 (s, 3 H), 1.01 (t, *J* = 7.0 Hz, 3 H); ir (mull):  $\nu$  max 3499, 3438, 1605, 1595, and 1586 cm<sup>-1</sup>; ms: M<sup>+</sup> 382, other ions at *m/z* 353, 324, 297, 227, 168, 142, 115, 91.

*Anal.* Calcd. for  $C_{22}H_{26}N_2O_2S \cdot HCl$ : C, 63.07; H, 6.50; N, 6.69. Found: C, 62.77; H, 6.52; N, 6.47.

The other enantiomer was prepared from **13b** (4.87 g, 10 mmoles), using the same procedure described above, to yield **14b** as an off-white solid (3.78 g, 90%): mp 273-274°;  $^1H$  nmr, ir, and ms are identical to those of **14a**.

*Anal.* Calcd. for  $C_{22}H_{26}N_2O_2S \cdot HCl$ : C, 63.07; H, 6.50; N, 6.69. Found: C, 62.91; H, 6.71; N, 6.57.

(*R*)-3-*p*-Toluenesulfonyl-6,7,8,9-tetrahydro-*N,N*-dipropyl-3*H*-benz[e]indol-8-amine Hydrochloride (**15a**) and Its (*S*)-Enantiomer (**15b**).

A mixture of **14a** (1.17 g, 2.8 mmoles), iodopropane (1.1 ml, 11.2 mmoles), and sodium carbonate (1.5 g, 14.0 mmoles) in acetonitrile (56 ml) was refluxed (bath temperature 90°) for 24 hours. The solvent was removed *in vacuo* and the concentrate was treated with water and extracted with methylene chloride (2 x 600 ml). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 400 g silica gel, eluting with hexane/acetone (2:1), and collecting 40 ml fractions. Fractions homogeneous by tlc were combined and concentrated *in vacuo* to yield **15a** as a light yellow oil (1.1 g, 93%). About 0.1 g of this oil was converted into the hydrochloride salt and recrystallized from ethyl acetate/hexane to give a white solid, mp 200-201°;  $^1H$  nmr:  $\delta$  7.79 (d,  $J = 8.4$  Hz, 1 H), 7.72 (d,  $J = 8.4$  Hz, 2 H), 7.57 (d,  $J = 3.5$  Hz, 1 H), 7.22 (d,  $J = 8.4$  Hz, 2 H), 7.05 (d,  $J = 8.4$  Hz, 1 H), 6.64 (d,  $J = 3.5$  Hz, 1 H), 3.70-1.82 (m, 15 H), 2.34 (s, 3 H), 1.03 and 1.01 (two t,  $J = 7.0$  Hz, 6 H); ir (mull):  $\nu$  max 1623 and 1595  $cm^{-1}$ ; ms:  $M^+$  424, other ions at  $m/z$  395, 324, 297, 269, 240, 168, 154, 142, 115, 91.

*Anal.* Calcd. for  $C_{25}H_{32}N_2O_2S \cdot HCl$ : C, 65.13; H, 7.22; N, 6.08. Found: C, 64.73; H, 7.49; N, 6.07.

The other enantiomer was prepared from **14b** (1.26 g, 3.0 mmoles), using the same procedure described above, to yield **15b** as a light yellow oil (3.78 g, 90%). About 0.1 g of this oil was converted into the hydrochloride salt and recrystallized from ethyl acetate/hexane to give a white solid: mp 201-202°;  $^1H$  nmr, ir, and ms are identical to those of **15a**.

*Anal.* Calcd. for  $C_{25}H_{32}N_2O_2S \cdot HCl$ : C, 65.13; H, 7.22; N, 6.08. Found: C, 64.82; H, 7.29; N, 6.04.

(*R*)-6,7,8,9-Tetrahydro-*N,N*-dipropyl-3*H*-benz[e]indol-8-amine (**16a**) and Its (*S*)-Enantiomer (**16b**).

A mixture of **15a** (1.17 g, 2.8 mmoles) and 4.37 *M* sodium methoxide/methanol (5.5 ml, 24.0 mmoles) in methanol/THF (2:1) (24 ml) was refluxed (bath temperature 80°) for 24 hours. The solvent was removed *in vacuo* and the concentrate was treated with water and extracted with methylene chloride (2 x 600 ml). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 400 g silica gel, eluting with hexane/acetone (2:1), and collecting 40 ml fractions. Fractions homogeneous by tlc were combined and concentrated *in vacuo* to give pure **16a** as a light yellow oil (0.6 g, 92%):  $^1H$  nmr:  $\delta$  8.29 (broad s, 1 H), 7.21 (d,  $J = 3.5$  Hz, 1 H), 7.19 (d,  $J = 8.4$  Hz, 2 H), 6.92 (d,  $J = 8.4$  Hz, 1 H), 6.51 (d,  $J = 3.5$  Hz, 1 H), 3.42-1.58 (m, 15 H), 0.94 (t,  $J = 7.0$  Hz, 6 H). No analytical data was necessary since this compound was already reported in literature [3,4].

The other enantiomer was prepared from **15b** (1.0 g, 2.4 mmoles), using the same procedure described above, to yield **16b** as a light yellow oil (0.6 g, 92%):  $^1H$  nmr is identical to that of **16a**.

(*R*)-(+)-1-Formyl-6,7,8,9-tetrahydro-*N,N*-dipropyl-3*H*-benz[e]indol-8-amine Fumarate (**1a**) and Its (*S*)-(-)-Enantiomer (**1b**).

A solution of **16a** (0.5 g, 1.9 mmoles) in DMF (8 ml) was treated with phosphoryl oxychloride (0.22 ml, 2.3 mmoles at 0° and the mixture was heated at 70°) for 2 hours. The mixture was cooled to room temperature, treated with 20% sodium hydroxide until  $pH > 13$ , and diluted with water. The mixture was extracted with ethyl acetate (2 x 1 l). The combined organic layers were washed with water, brine, dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The crude product was purified by liquid chromatography on 400 g silica gel, eluting with acetone (1 l) followed by 5% 2-propanol in acetone, and collecting 40 ml fractions. Fractions homogeneous by tlc were combined and concentrated to yield a yellow oil (0.46 g, 81%). This oil was converted into the fumarate salt by dissolving this oil with equivalent amount of fumaric acid (0.185 g, 1.6 mmoles) in hot 2-propanol, concentrated and diluted with ether and the mixture was allowed to stand in the freezer to yield **1a** as a red colored solid (0.46 g), mp 177-178°;  $^1H$  nmr (perdeuteriomethanol):  $\delta$  9.76 (s, 1 H), 8.13 (s, 1 H), 7.30 (d,  $J = 8.4$  Hz, 1 H), 7.08 (d,  $J = 8.4$  Hz, 1 H), 6.68 (s, 2 H), 4.22-1.75 (m, 15 H), 1.06 (t,  $J = 7.0$  Hz, 6 H); ir (mull):  $\nu$  max 3206, 2856, 2728, 1705, 1659, 1599 and 1573  $cm^{-1}$ ; ms:  $M^+$  298, other ions at  $m/z$  269, 241, 198, 182, 170, 143, 116;  $[\alpha]_D^{25} + 112.5^\circ$  (c 0.96, methanol) [lit +112°] [3].

*Anal.* Calcd. for  $C_{19}H_{26}N_2O \cdot C_4H_4O_4$ : C, 66.65; H, 7.30; N, 6.76. Found: C, 66.61; H, 7.49; N, 6.38.

The other enantiomer was prepared from **16b** (0.5 g, 1.9 mmoles), using the same procedure as described above, to yield a light yellow oil (0.52 g, 90%). This oil was converted into the fumaric acid salt and recrystallized from ether/2-propanol to give **1b** as an orange colored solid: mp 176-177°;  $^1H$  nmr, ir and ms are identical to those of **1a**;  $[\alpha]_D^{25} - 113.3^\circ$  (c 1.13, methanol) [lit -112°] [3].

*Anal.* Calcd. for  $C_{19}H_{26}N_2O \cdot C_4H_4O_4$ : C, 66.65; H, 7.30; N, 6.76. Found: C, 66.48; H, 7.20; N, 6.57.

X-ray Crystallography of **11c**.  $C_{27}H_{28}N_2O_2S \cdot HCl$  0.5(0.6x $C_4H_8O_2$ ); formula weight = 507.5; monoclinic; space group C2;  $Z = 4$ ;  $a = 29.458$  (2),  $b = 7.227$  (3),  $c = 16.614$  (7) Å,  $\beta = 128.45$  (2)°  $V = 2770$  (1) Å<sup>3</sup>; calculated density = 1.22 g  $cm^{-3}$ , absorption coefficient  $\mu = 2.0$   $mm^{-1}$ . Intensity data were collected on a clear prism 0.08 x 0.11 x 0.25 mm mounted on a glass fiber on a Siemens P1bar diffractometer. Graphite monochromatized  $CuK\alpha$  radiation was used,  $[\lambda(CuK\alpha) = 1.5418$  Å], with maximum  $2\theta = 121^\circ$ . Intensity data were measured at room temperature using  $\theta/2\theta$  scans with scan widths  $\geq 3.2^\circ$  and a scan rate of 2°/min. The total time spent counting background, half at each end of the scan, was equal to the time spent scanning. Of 2284 unique reflections measured, 1618 had intensities  $> 3\sigma$ . Ten reflections periodically monitored showed no trend towards deterioration;  $\sigma^2(I)$  was approximated by  $\sigma^2(I)$  from counting statistics + (0.0271)<sup>2</sup>, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least squares fit of  $K\alpha_1$   $2\theta$  values ( $\lambda K\alpha_1 = 1.5402$ ) for 25 high  $2\theta$  reflections [13]. A Lp correction appropriate for a monochromator with

50% perfect character was applied, and the data were corrected for absorption [14].

The structure was solved by direct methods, using MULTAN80 [15]. There is a disordered ethyl acetate molecule, approximately 60% populated, positioned so that the ether oxygen is on the 2-fold axis. Least squares refinement included coordinates for all atoms and anisotropic thermal parameters for nonhydrogen atoms, except that the disordered solvent atoms were kept isotropic and given carbon form factors. All hydrogens except those on the disordered ethyl acetate were found in difference maps close to generated positions; generated positions were used in the calculations and updated after each refinement. Temperature factors for hydrogens were assigned as one-half unit higher than the equivalent isotropic temperature factors for the attached carbon. The function minimized in the refinement was  $\sum w(F_o^2 - F_c^2)^2$ , where weights  $w$  were  $1/\sigma^2(F_o^2)$ . In the final refinement anomalous dispersion factors [16] were included; in the final cycle all shifts were  $\leq 0.3\sigma$ . The absolute configuration was determined by the method of Bijvoet [17] to be *S* at position 8, the point of attachment of the *N*-methylbenzylamine, and *R* at the benzylamine  $\alpha$  carbon. Accurate measurements of 12 reflections which were very strongly influenced by anomalous dispersion, each one measured at all accessible symmetry related positions (24 Friedel pairs), were compared. All 24 comparisons indicated unequivocally that the enantiomer shown is the correct one. The final agreement index *R* was 0.099 for 2282 reflections (2 intense reflections were given zero weight in the refinement), and 0.078 for the 1618 reflections having  $F_o^2 \geq 3\sigma$ . The standard deviation of fit was 3.1. There were hydrogen bonds between the protonated secondary amine and two chlorines, the chlorine at *x,y,z* and a symmetry related chlorine at *0.5-x, y-0.5, 1.0-z*; N-Cl distances are 3.100(9)Å and 3.144(7)Å. Atomic form factors were from Doyle and Turner [18], and for hydrogen, from Stewart, Davidson, and Simpson [19]. The CRYM system of computer programs was used [20].

The atomic coordinates and thermal parameters of **11c** are shown in Tables 1 and 1a, and the bond lengths, angles, and torsion angles are listed in Table 2. The close intermolecular contacts between non-hydrogen atoms and hydrogen bonds for **11c** are shown in Tables 3 and 4, respectively.

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