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A Concise Silylamine Approach to 2-Amino-3-hydroxy-indoles with Potent *in vivo* Antimalaria Activity

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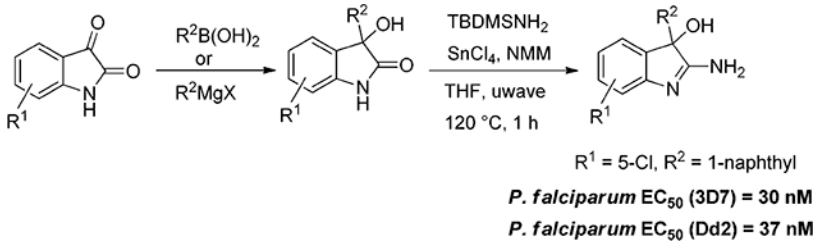
Graphical Abstract



The development of a concise strategy to access 2-amino-3-hydroxy-indoles, which are disclosed as novel antimalarials with potent *in vivo* activity, is reported. Starting from isatins the target compounds are synthesized in 2 steps and in good yields via oxoindole intermediates by employing *tert*-butyldimethylsilyl amine (TBDMSNH2) as previously unexplored ammonia equivalent.

Malaria is the most deadly parasitic infectious disease with an estimated 300–500 million cases and a death toll of 0.8–1.2 million in 2008 alone.[1]Of the four *Plasmodium* species that are relevant for humans, *P. falciparum* accounts for most of the fatalities.[1]These already grim statistics are likely to become even grimmer as *P. falciparum* strains that are resistant to

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Supporting Information Available: Experimental procedures and characterization; ^{1}H and ^{13}C NMR, chiral SFC chromatogram, and X-ray structure of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

commonly used antimalaria chemotherapeutic agents emerge and spread throughout Africa and parts of Asia.

The most recent antimalarial drug class was introduced in 1996[2] In an effort to address the urgent need for new drugs, especially ones with new cellular targets or chemo types that could delay the emergence of resistance, we have screened small-molecule libraries for novel, drug-like compounds with whole-cell antimalarial activity and limited susceptibility to established mechanisms of drug resistance.[3] Very recently, two similar efforts have also been reported.[4,5] Out of ~ 79,000 compounds,[6] 104 inhibitors with nanomolar activity against drug-sensitive (3D7) and multidrug-resistant (Dd2, HB3) *P. falciparum* strains were identified.[3] One of the hits, the 2-amino-5-chloro-3-hydroxy-3-phenylindole **1a** (see Figure 1) was particularly attractive because of its unusual and compact 2-amino-3-hydroxy-indole core structure. In addition, compound **1a** achieved excellent exposure in mouse pharmacokinetic studies, and more importantly, when tested in a 4-day suppressive *P. berghei* mouse model **1a** demonstrated very good *in vivo* efficacy,[7] causing a dose dependent decrease in parasitemia with undetectable levels of parasites at the highest dose tested and no signs of adverse side effects (Figure 1).

Encouraged by this promising *in vivo* activity we began to explore and optimize this compound class. A thorough literature survey revealed that 2-amino-3-hydroxy-indoles are virtually unexplored for biological activity, which we suspect results at least in part from the limited synthetic methodology to access this class. To date, four distinct approaches have been reported.[8–11]We found the methods reported by Bell et al. to prepare the 2-amino-3-hydroxy-indoles V*ia* reaction of KCN with formylated or dichloroacylated 2-aminobenzophenones to be the most appropriate (Scheme 1).[9]

Unfortunately, this strategy, although readily scalable and attractive for process scale syntheses, is limited for early stage exploratory medicinal chemistry due to the lack of commercially available 2-aminobenzophenones and the inherent lack of enantioselectivity. As a result, we developed a general, short and efficient method that would (a) provide analogues in quantities that satisfy early stage drug discovery requirements, (b) tolerate a wide variety of functional groups, (c) begin with commercially available diversely functionalized building blocks, and (d) avoid the use of cyanide while (e) offering the potential to enantioselectively access 2-aminy-3-hydroxy-indoles.

We envisioned a three-step reaction sequence starting from isatins, which are widely available and inexpensive starting materials as shown in Scheme 2.

Grignard addition or Rh-catalyzed addition[12] of boronic acids to isatin **2** would give 3-hydroxy-3-aryl-oxindole **3**. Oxindole **3** could then react with a protected ammonia equivalent (e.g., allylamine) to yield the corresponding protected 2-amino-3-hydroxy-indole **4**, which on deprotection would result in the desired 2-amino-3-hydroxy-indole **1**. Furthermore, boronic acids[13] and electron-rich arenes[14] can be added to isatins with high enantioselectivity. This method would also allow access to 2-amino-3-hydroxy-indoles enantioselectively.

On the basis of the well-precedented nature of the first step, we directed our efforts toward the conversion of 3-hydroxyoxindoles **3** to allyl-protected 2-amino-3-hydroxy-indoles **4**. We were somewhat encouraged by variable conversions (~30–50%) obtained upon heating 5-chloro-3-hydroxyoxindole **3a** with an excess of allylamine in the presence of 5 mol % of PTSA and 4 Å molecular sieves.[15] Attempts to increase the yields by employing other drying agents such as Na_2SO_4, $MgSO_4$ or the use of Dean-Stark apparatus were not successful. We anticipated that better conversions could be achieved with the use of a Lewis acid, which not only would catalyze the transformation but would also efficiently entrap the water formed. Exploring a set of Lewis acids confirmed our hypothesis, with both $SnCl_4$ and $Ti(O\mathit{i}Pr)_4$ efficiently and more importantly, reproducibly promoting the conversion of **3a** to **4a** (Scheme 3). Furthermore, while microwave conditions reduced the reaction times from 12–18 h to 40–60 min, the addition of NMM (N-methyl morpholine) as an acid scavenger allowed the amine coupling partner to be used in nominal amount.

Disappointingly, the deprotection of the allyl group in **4a** proved challenging despite the plethora of deallylation protocols for amines and amides.[16,17]

Next, we turned our attention to identifying an ammonia equivalent that would allow for more facile deprotection. On the basis of literature precedents of employing a silylated ammonia equivalent in unrelated transformations,[18] we decided to explore commercially available Ph_3SiNH_2. Unexpectedly, as shown in Scheme 3, the reaction of **3a** with Ph_3SiNH_2 under the optimized conditions produced *O*-silylated 2-amino-3-hydroxy-indole **5**, in 60% yield while only trace amounts of the desired desilylated product **1a** were observed. Aminoindole **5** is probably formed by the intramolecular migration of the silyl group. Attempts to desilylate **5** using TBAF or other fluoride sources resulted in hydrolysis of **5** and in recovery of the original hydroxyoxindole starting material **3a**.

Encouraged by the finding that a silylamine appears well-suited to install the desired amine functionality, we suspected that less sterically demanding analogues of Ph_3SiNH_2 such as *tert*-butyldimethylsilyl amine ($TBDMSNH_2$) might allow deprotection under condition that would prevent hydrolysis of the amine. Pleasingly, we were able to directly isolate the desired 2-aminoindole product **1a** in 60% isolated yield. The structure of **1a** was unambiguously established by X-ray analysis revealing that the newly installed substituent appears to favor the tautomer with an exoamine rather than an exoimine geometry (see Supporting Information).

Although $TBDMSNH_2$ has been utilized in the context of its ligand attributes for metal complexes,[19–21] this is, to our knowledge, the first report on the application of $TBDMSNH_2$ in organic synthesis.

The synthetic utility of this novel $SnCl_4$-promoted amidation reaction with $TBDMSNH_2$ as an ammonia surrogate was then explored using a series of substituted 3-hydroxy-oxindoles. A variety of functional groups in the indole ring, including halogens, nitro, and alkyl ether are well tolerated in the amidation process (Table 1). The amidation reaction worked equally well under $Ti(O\mathit{i}Pr)_4$ promoted conditions.

The substrate scope with respect to the substituent at the 3-position of oxindoles was also found to be broad. Thus, the aryl group at the 3-position possessing functional groups such as ester (entry h) and alkyne (entry d) could be employed in this process. In the case of an aryl group substituted with an enolizable ketone, the use of $Ti(O\mathit{i}Pr)_4$ in lieu of $SnCl_4$ was critical for the success of the reaction (entry i, Table 1), as is the indole with free nitrogen as R^2 (entry p).

Interestingly, an aryl group substituted with the sulfonamide group yielded the aminoindole with TBDMS group on sulfonamide nitrogen with this method. However, deprotection with HF/pyridine gave the aminoindole **1q** (entry q). It is worth noting that several of these 2-amino-3-hydroxy-indoles would be difficult to access or would require functional group manipulations via a cyanohydrin route significantly lengthening the synthesis. In addition, our methodology allowed for direct access of *N*(1)-alkyl iminoindole using the corresponding oxindole as starting material (entry r).

To ascertain whether an enantioenriched 3-hydroxyoxin-dole would transform into 2-amino-3-hydroxy-indole under the reaction conditions without any loss in enantiomeric excess, we prepared chiral 3-hydroxyoxindole (*S*)-**3a**[22](>95% ee) and subjected it to $SnCl_4$ promoted amidation reaction with $TBDMSNH_2$. Gratifyingly, the corresponding 2-amino-3-hydroxy-indole (*S*)-**1a** was obtained in good yield without any measurable loss of enantiomeric excess (>95%ee) indicating no racemization occurred during the reaction (Scheme 4).

The initial exploratory SAR against drug-sensitive (3D7) and drug-resistant (Dd2) parasite strains indicates that 2-amino-3-hydroxy-indoles are in general more active when R^2 is either an *ortho*-substituted electron-rich aromatic ring (entries c and m, Table 1) or a naphthyl moiety (entry n, Table 1), which is possibly a result of the increased dihedral angle of the biaryl system and thereby generating a more favorable binding conformation for its target(s). 2-Amino-3-hydroxy-indoles **1** with benzylic and alkyl groups at R^2 also displayed potent antimalarial activity for R^1 as 5-Cl. Furthermore, protection of the 3-hydroxyl (Scheme 3 compound **5**; EC_{50} >5 μM) or 2-amino groups (Scheme 3 compound **4a**; EC_{50} > 5 μM) was found to be detrimental. The 3-hydroxyl-oxindoles (**3**) which potentially can be regenerated by hydrolysis of the 2-amino group did not exhibit any significant antimalarial activity.

A 2-fold difference in *in Vitro* activity between the two enantiomers of **1a** was noted and interestingly, racemate was found to be more active than either of the two enantiomers (Scheme 4).

In summary, we have identified 2-amino-3-hydroxy-indoles as a novel chemical class with potent *in Vitro* and *in vivo* antimalaria activity. We have developed a concise synthetic strategy to efficiently synthesize analogues in quantities sufficient for medicinal chemistry exploration. This method establishes the unprecedented use of $TBDMSNH_2$ as an ammonia surrogate and allows for the first enantioselective synthesis of 2-amino-3-hydroxy-indoles. It is likely that $TBDMSNH_2$ will find use in other transformations requiring protected ammonia equivalents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment.

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References

(1). Aregawi M Cibulskis R Otten M Williams R Dye C World Malaria Report 2008; World Health Organization: Geneva, 2008.

(2). Ekland EH; Fidock DA Int. J. Parasitol 2008, 38, 743. [PubMed: 18406409]

(3). Baniecki ML; Wirth DF; Clardy J Antimicrob. Agents Chemother 2007, 51, 716. [PubMed: 17116676]

(4). Gamo F-J; Sanz LM; Vidal J; Cozar C. d.; Alvarez E; Lavandera J-L; Vanderwall DE; Green DVS; Kumar V; Hasan S; Brown JR; Peishoff CE; Cardon LR; Garcia-Bustos JF Nature 2010, 465, 305. [PubMed: 20485427]

(5). Guiguemde WA; Shelat AA; Bouck D; Duffy S; Crowther GJ; Davis PH; Smithson DC; Connelly M; Clark J; Zhu F; Jiménez-Díaz MB; Martinez MS; Wilson EB; Tripathi AK; Gut J; Sharlow ER; Bathurst I; El Mazouni F; Fowble JW; Forquer I; McGinley PL; Castro S; Angulo-Barturen I; Ferrer S; Rosenthal PJ; Derisi JL; Sullivan DJ; Lazo JS; Roos DS; Riscoe MK; Phillips MA; Rathod PK; Van Voorhis WC; M Avery V; Guy RK Nature 2010, 465, 311. [PubMed: 20485428]

(6). Analysis of screening libraries and assay results was supported by Instant JChem, JKlustor, and Screen; ChemAxon: Budapest, Hungary; www.chemaxon.com/products.html.

(7). Peters W Robinson BL In Parasitic Infection Modelsin; Zak O, Sande MA, Eds.; Academic Press: London, 1999; pp 757.

(8). Wittig G; Kleiner H; Conrad J Liebigs Ann. Chem 1929, 469, 1.

(9). Bell SC; Wei PHL J. Heterocycl. Chem 1969, 6, 599.

(10). Ishizumi K; Inaba S; Yamamoto H J. Org. Chem 1974, 39, 2581.

(11). Benincori T; Sannicolo F J. Org. Chem 1988, 53, 1309.

(12). Toullec P; Jagt R; de Vries J; Feringa B; Minnaard A Org. Lett 2006, 8, 2715. [PubMed: 16774239]

(13). Shintani R; Inoue M; Hayashi T Angew. Chem., Int. Ed 2006, 45, 3353.

(14). Hanhan NV; Sahin AH; Chang TW; Fettinger JC; Franz AK Angew. Chem., Int. Ed 2010, 49, 744.

(15). Meyer R; Zwiesler M J. Org. Chem 1968, 33, 4274.

(16). Escoubet S; Gastaldi S; Bertrand M Eur. J. Org. Chem 2005, 2005, 3855.

(17). Unsatisfactory yields were obtained when a $RhCl_3$-catalyzed allyl deprotection strategy was applied. Zacuto M; Xu F J. Org. Chem 2007, 72, 6298. [PubMed: 17625881]

(18). Huang X; Buchwald S Org. Lett 2001, 3, 3417. [PubMed: 11594848]

(19). West R; Boudjouk P J. Am. Chem. Soc 1973, 95, 3983.

(20). Bowser J; Neilson R; Wells R Inorg. Chem 1978, 17, 1882.

(21). Quallich G; Makowski T; Sanders A; Urban F; Vazquez E J. Org. Chem 1998, 63, 4116.

(22). Hewawasam P; Erway M; Moon S; Knipe J; Weiner H; Boissard C; Post-Munson D; Gao Q; Huang S; Gribkoff V; Meanwell N J. Med. Chem 2002, 45, 1487. [PubMed: 11906290]

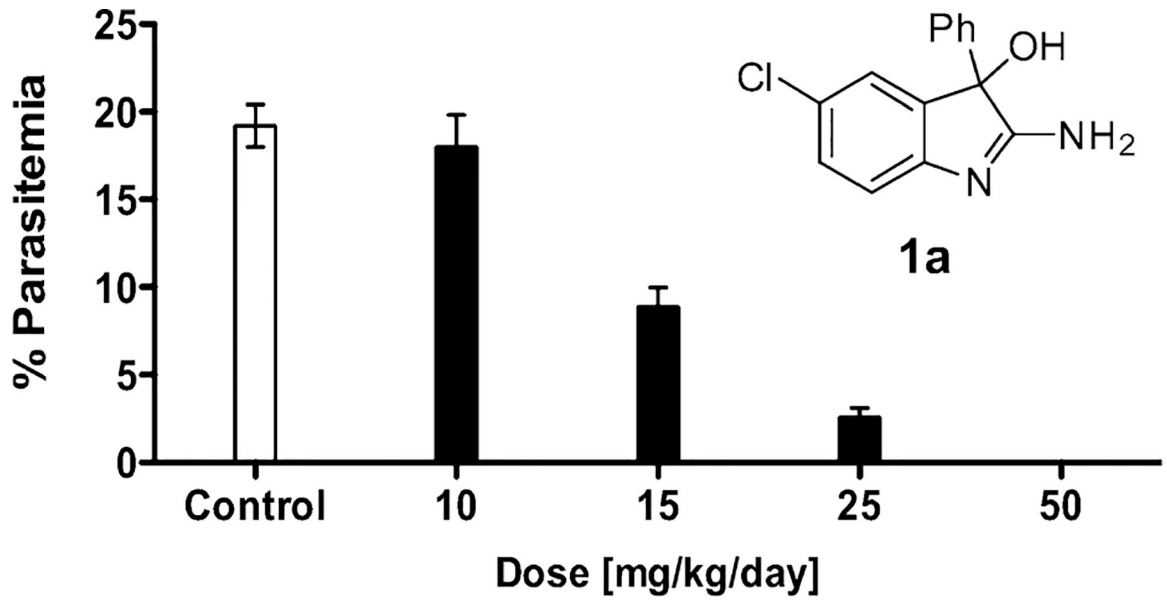
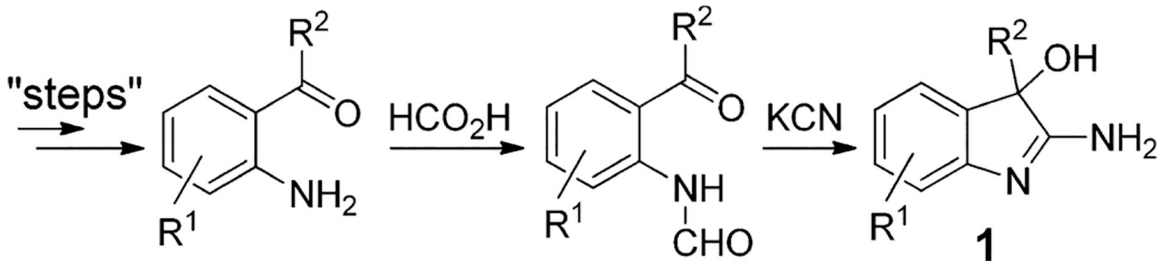


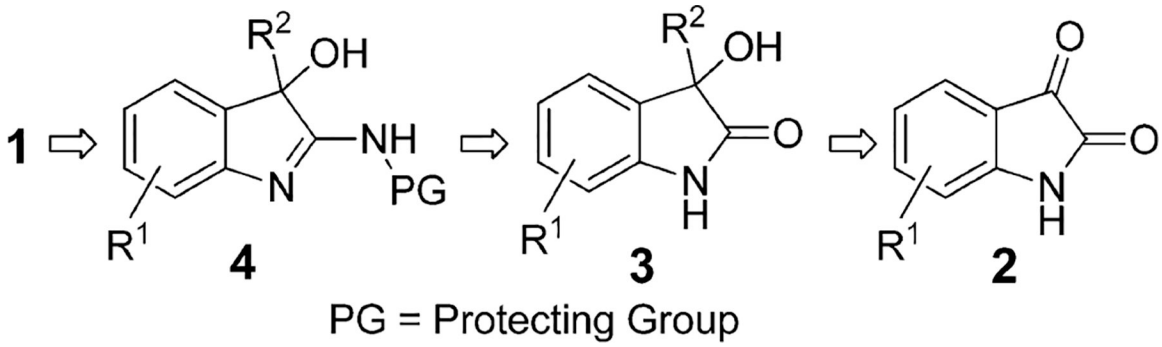
Figure 1.

In vivo antimalaria activity of 2-aminoindole **1a**. Following inoculation of Swiss Albino mice with *P. berghei* parasites, **1a** was administered i.p. once daily for 4 days, and parasitemia was determined on day 5.

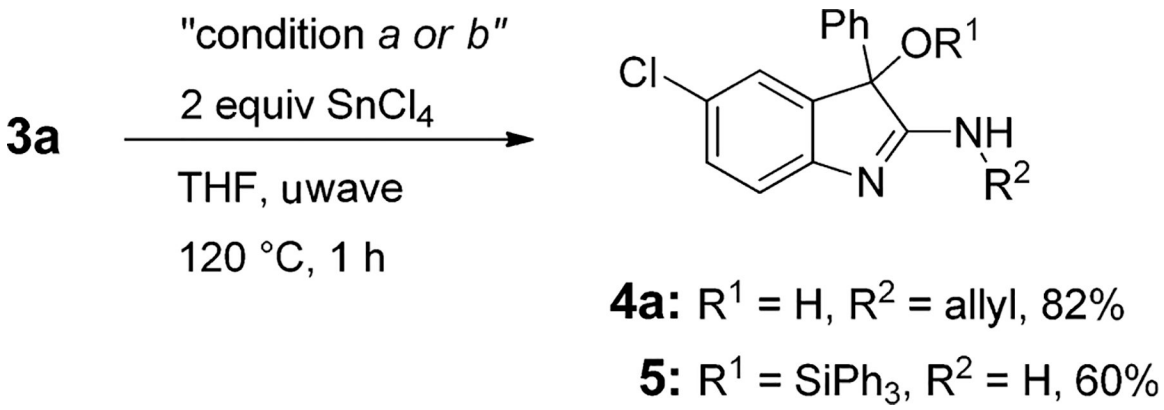


Scheme 1.

Traditional Synthetic Strategy to Access 2-Amino-3-hydroxy-indoles via Cyanohydrins



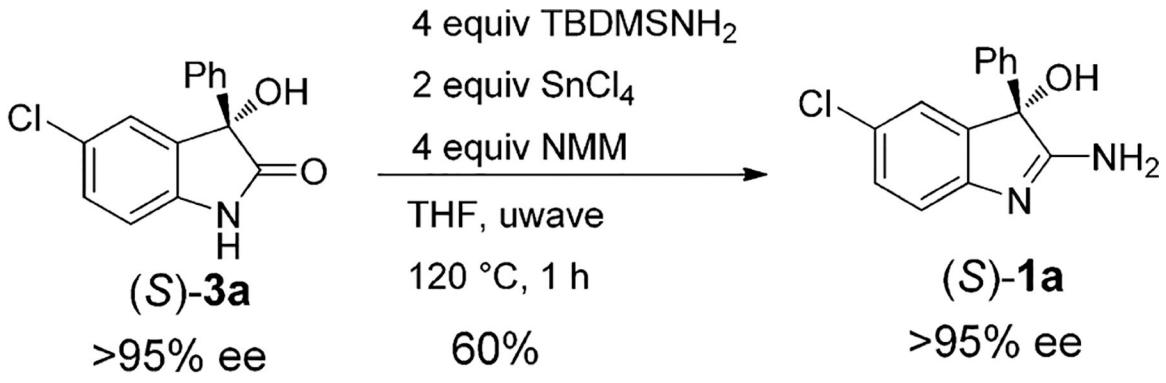
Scheme 2.
Retrosynthetic Analysis Starting from Isatin (**2**)



Scheme 3.

Amidations with Allylamine and Triphenylsilylamine Conditions[a]

a Conditions: (a) excess allylamine for **4a**, (b) 2 equiv of Ph_3SiNH_2 and 4 equiv NMM for **5**.

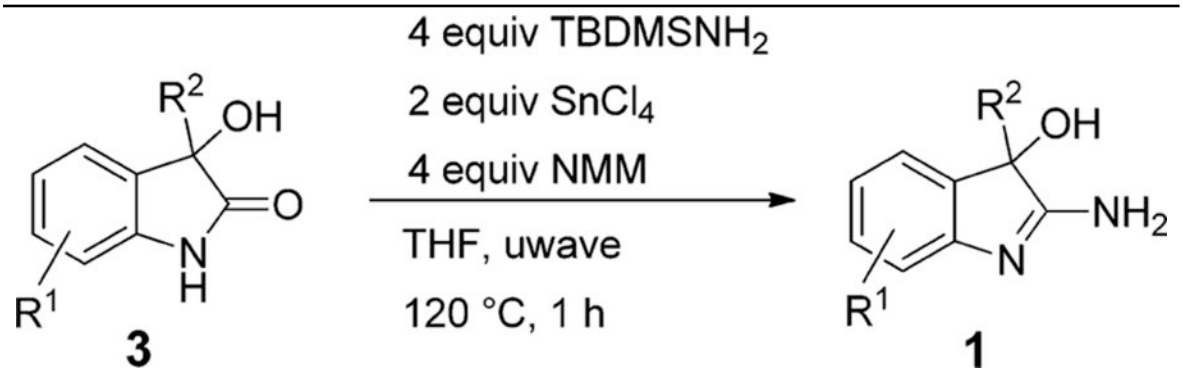


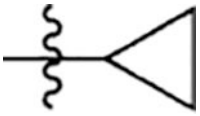
	EC50 (nM)	
enantiomer	3D7	Dd2
(*S*)-**1a**	665	1460
(*R*)-**1a**	313	675
rac-**1a**	216	507

Scheme 4.
Synthesis of Enantioenriched 2-Amino-3-hydroxy-indole **1a**

Table 1.

Direct Conversion of **3** to **1** with $TBDMSNH_2$



entry	R^1	R^2	yield (%)[a]	EC_{50} (nM)	
				3D7	Dd2
a	5-CI	Ph	60 (56)[b]	216	507
b	5-I	Ph	64	289	338
c	5-CI	*o*-OMePh	43	24	57
d	5-CI		45	1160	1127
e	5-CI		58	104	465
f	5-F	*p*-OMePh	52	85	359
g	5-CI	*iso*-butyl	50	232	270
h	5-CI	*m*-CO_2MePh	38	783	1578
i	5-CI	*m*-AcPh	30[b]	529	1525
j	5-CI	CH_2-(*o*-tolyl)	53	63	139
k	4-Br	CH_2Ph	51	>5000	>5000
l	5-OMe	Ph	49 (48)[b]	24	385
m	H	*o*-tolyl	53	112	152
n	5-CI	1-naphthyl	67	30	37
o	5-NO_2	Ph	30[b]	>5000	>5000
p	5-CI	3'-(5'-OMe-indolyl)	40[b]	>5000	>5000
q	5-CI	*p*-SO_2NH_2Ph	45[b,c]	>5000	>5000
r[d]	H	Ph	39	>5000	>5000
		Chloroquine		16	216

[a] Isolated yields.

[b] $Ti(OiPr)_4$ was used instead of $SnCl_4$ and NMM.

[c] TBS-protected aminoindole was formed, which on treatment with HF/pyridine gave **1q**; yield reported is over two steps.

[d] The indole nitrogen is methylated (see Supporting Information).