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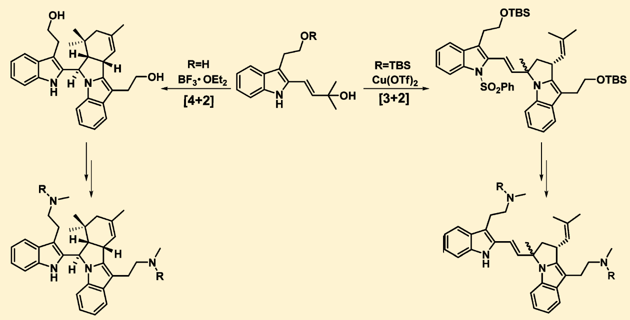
Biomimetic Total Syntheses of Borreverine and Flinderole Alkaloids

Dattatraya H. Dethe,* Rohan D. Erande, and Alok Ranjan

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur-208016, India

S Supporting Information

ABSTRACT: Dimeric indole alkaloids represent a structurally unique class of natural products having interesting biological activities. Recently, we reported the first total synthesis of flinderoles B and C, structurally unique and potent antimalarial natural products. Central to the design of the approach and by virtue of a one-pot, acid-catalyzed dimerization reaction, the route also provided total synthesis of the borreverine class of natural products. This full account details the progress of efforts that culminated in the protecting-group-free, six-step total synthesis of all of the flindersia alkaloids: dimethylisoborreverine, isoborreverine, flinderoles A–C, and their analogues. A biomimetic approach featuring a scalable and catalytic formal [3 + 2] cycloaddition and Diels–Alder reaction is outlined in detail. On the basis of the experimental observations, a detailed mechanism has been proposed for the dimerization of tertiary alcohol **28**.



Isoborreverine, (5, R = H)
Dimethylisoborreverine, (6, R = CH_3)

Flinderole-A, (1, α–Me, R = H)
Flinderole-B, (2, α–Me, R = CH_3)
Flinderole-C, (3, β–Me, R = CH_3)

■ INTRODUCTION

Synthetic chemists are always fascinated by biomimetic synthesis[1] of natural products, as it allows them to achieve the synthesis of complex natural products in the most efficient way comprising the minimum number of synthetic steps and economically viable large-scale synthesis for further biological and pharmaceutical studies. Multidrug-resistant parasites have driven the quest for the development of new classes of antimalarial agents with novel modes of action. Natural products (quinine and artimisinin) have proven to be important leads in this regard,[2] due to the development of modern synthetic tools to assemble such natural products in the laboratory to readily access a series of analogues for structure–activity relationships (SARs). Recently, Avery and co-workers[3] have reported the isolation of new class of antimalarial agents, flinderole A (**1**), from the bark of *F. Acuminata*, while flinderoles B (**2**) and C (**3**) were obtained from *F. Ambiosis* along with the previously known compounds borrerine (**4**), borreverine (**7**), isoborreverine (**5**), and dimethylisoborreverine (**6**) (Figure 1). Borrerine (**4**) was first isolated in 1973 by Goutarel et al.[4] Borreverine (**7**), isoborreverine (**5**), and dimethylisoborreverine (**6**) were isolated in 1977 by Riche et al.[5] The structures of borreverine (**7**) and isoborreverine (**5**) were established by single-crystal X-ray analysis. Another natural product possessing the borreverine skeleton, spermacoceine (**8**), was isolated by the research group of Balde et al.[6] in 1991 from *Borreria verticillata*. Flinderoles A–C, isoborreverine, and dimethylisoborreverine have shown selective antimalarial activity, with IC_{50} values between 0.08 and 1.42 μm against the chloroquine-resistant *P. falciparum* strain. Dimethylisoborreverine was the most active (IC_{50} = 80 nm) and selective among all the flindersia alkaloids screened. Detailed biological activity studies by the Avery group[7] have shown that these alkaloids inhibit parasitic hemoglobin metabolism through a mode of action different from that of chloroquine. The biomimetic pathway proposed by Koch et al.[8] for the synthesis of borreverine and by our group[9] for the synthesis of flinderoles is depicted in Scheme 1. The co-occurrence of borrerine (**4**) and borreverine (**7**) in *Borreria verticillata* suggested that biosynthetically borreverine (**7**) and isoborreverine (**5**) might have been prepared by dimerization of borrerine (**4**). The interesting and novel chemical structures and vitally important biological activity of flinderoles and borreverines made them attractive targets for total synthesis, and a number of groups have reported their synthetic studies toward this end. Following our initial report on the first total synthesis of flinderoles B and C,[9] Toste et al.[10] and May et al.[11] have reported alternative elegant approaches. The route devised by the Toste group employed a gold(I)-catalyzed hydroarylation of an allene with indole; further reactions were then carried out to produce the final products flinderoles B and C. May et al. devised a third route that required just three steps for the total synthesis of flinderoles A–C by acid-catalyzed dimerization of borrerine (**4**). In 1979, Koch et al.[8] reported the biomimetic synthesis of borreverine (**7**) and isoborreverine (**5**) by the trifluoroacetic acid mediated dimerization of borrerine (**4**). We present here a concise total synthesis of isoborreverine (**5**) and dimethylisoborreverine (**6**) along with an improved protecting-group-free synthesis of flinderoles A–C.

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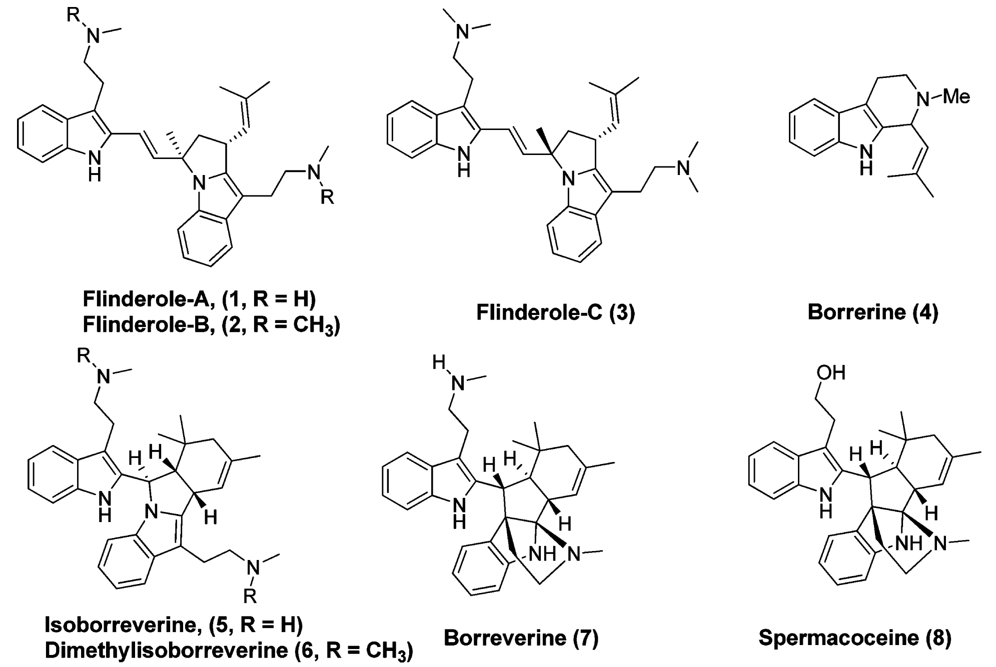
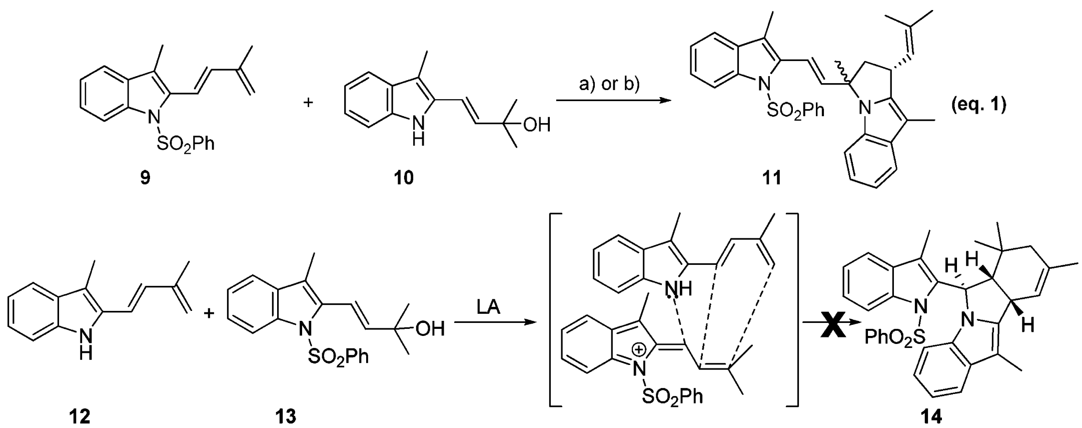


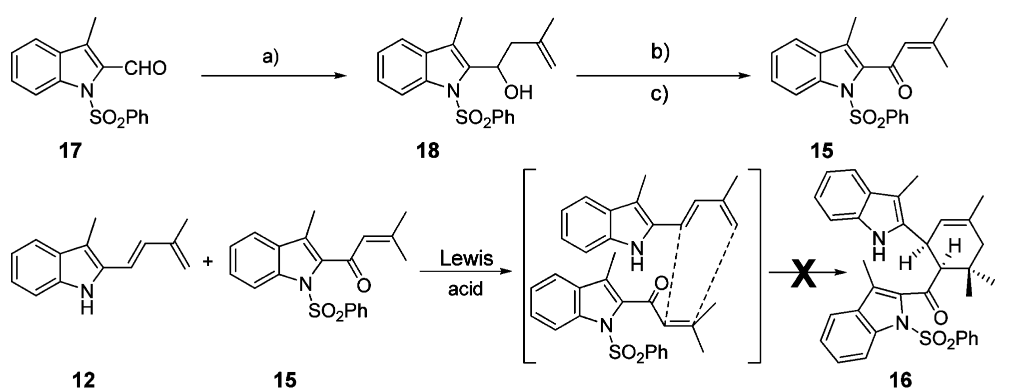
Figure 1. Structures of borreverine and flinderole natural products.

Scheme 1. Protecting Group Switch Strategy for Synthesis of Borreverines[a]



[a]Legend: (a) $Cu(OTf)_2$ (0.2 equiv), CH_2Cl_2, room temperature, 30 min, 95%; (b) $BF_3 \cdot OEt_2$ (0.2 equiv), CH_2Cl_2, room temperature, 20 min, 92%.

Scheme 2. Model Studies for the Synthesis of Isoborreverine[a]



[a]Legend: (a) 3-chloro-2-methylprop-1-ene (1.5 equiv), Mg turnings (1.5 equiv), I_2 (cat.), THF, room temperature, 2 h, 84%; (b) IBX (6.0 equiv), EtOAc, reflux, 3 h, 80%; (c) DBU (1.0 equiv), CH_2Cl_2, room temperature, 1 h, 90%.

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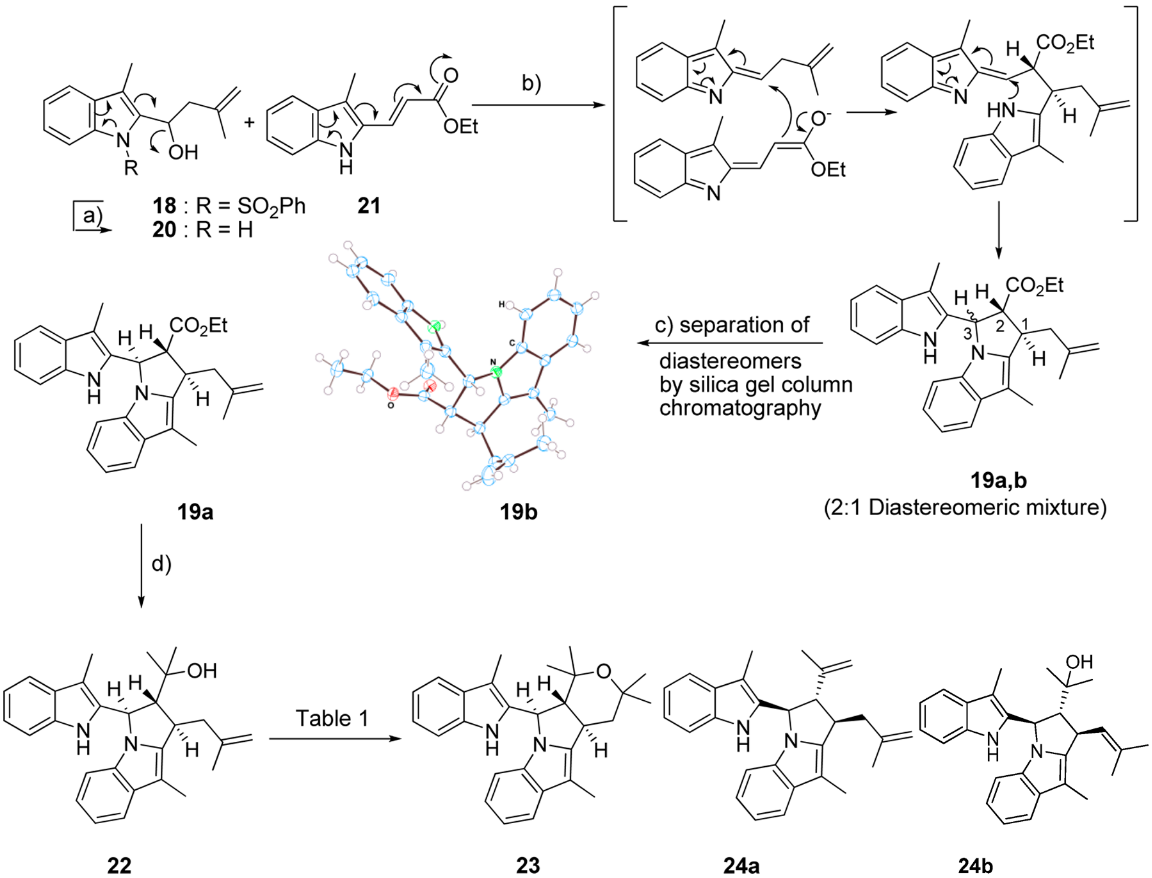
Scheme 3. Intermolecular Formal [3 + 2] Cycloaddition Reaction of Alcohol 20 and Ester 21[a]



[a]Legend: (a) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, room temperature, 1 h, 83%; (b) $BF_3{\cdot}OEt_2$ (0.2 equiv), CH_2Cl_2, room temperature, 5 min, 77%; (c) separation of diastereomers by silica gel column chromatography; (d) MeI (7.0 equiv), Mg turnings (6.0 equiv), I_2 (cat.), Et_2O, 0 °C to room temperature, 2 h, 85%.

Table 1. Screening of Catalyst for Ene Cyclization

entry	cat.	amt of cat. (mol %)	solvent	temp	time (h)	product	yield (%)
1	$BF_3{\cdot}OEt_2$	20	CH_2Cl_2	room temp	16	**23**	71
2	TFA	20	CH_2Cl_2	room temp	48	**22**	93
3	$Cu(OTf)_2$	20	CH_2Cl_2	room temp	48	**22**	87
4	$MsCl/Et_3N$	50	THF	reflux	2	**24a**	62
5	$TiCl_4$	80	CH_2Cl_2	room temp	4	**24b**	57
6	PTSA	100	CH_2Cl_2	room temp	24	**23**	70
7	PTSA	50	C_6H_6	reflux	2	**23**	62
8	CF_3SO_2H	20	CH_2Cl_2	room temp	$^1/_2$	**23**	70

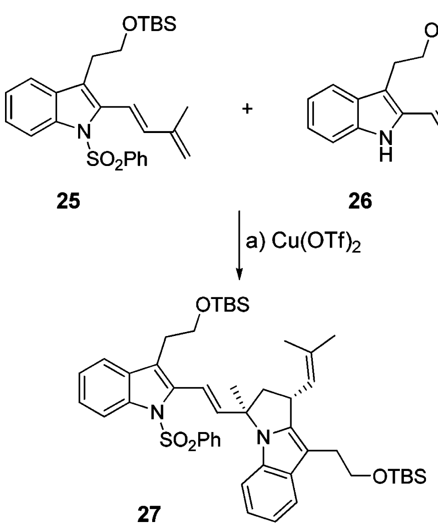
■ RESULTS AND DISCUSSION

Armed with the knowledge gained in our earlier synthesis of flinderoles,[9] we were ready to attempt the synthesis of the more complex natural products isoborreverine (**5**) and dimethylisoborreverine (**6**). According to our retrosynthetic plan, it was thought that if we do the phenylsulfonyl protecting group switch from diene **9** to tertiary alcohol **10** (Scheme 1, eq 1), it might lead to the formation of [4 + 2] cycloaddition product **14** instead of compound **11**, as shown in Scheme 1. However, to our disappointment, treatment of diene **12** with tertiary alcohol **13** only afforded the diene **9** by dehydration of tertiary alcohol **13**. In another direction it was contemplated that diene **12** would react with dienophile **15** to generate the Diels–Alder product **16**, which on further functional group transformation would lead to borreverine and isoborreverine cores. Synthesis of the dienophile **15** was initiated by addition of Grignard reagent to aldehyde **17**; oxidation of the alcohol **18** thus generated followed by isomerization of the double bond using DBU afforded the enone **15**. Again, to our disappointment under various reaction conditions diene **12** and enone **15** failed to undergo a Diels–Alder reaction (Scheme 2).

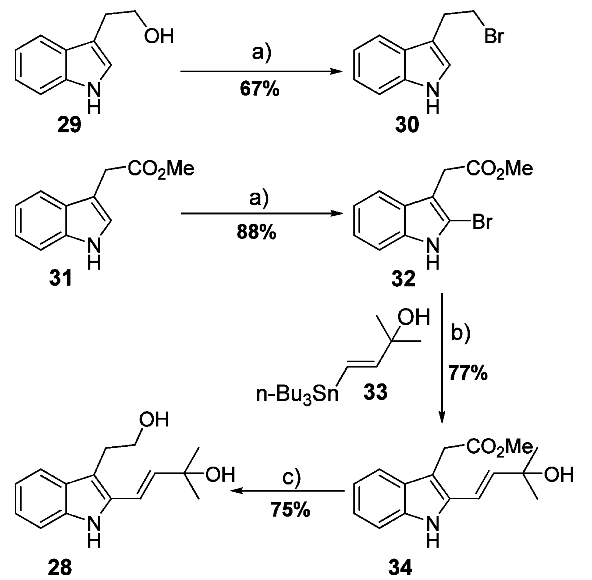
We then turned our attention toward another approach; it was envisioned that the isoborreverine skeleton could be generated from the suitably substituted pyrrolo[1,2a]indole derivative **22** by ene type cyclization or olefin cation cyclization. Compound **22** could be prepared from indolyl alcohol **20** and ester **21** by a formal [3 + 2] cycloaddition reaction followed by Grignard reaction. On the basis of our earlier experience,[9] it was assumed that the use of $BF_3{\cdot}OEt_2$ for formal [3 + 2] reaction would generate a mixture of diastereomers at the C-1 and C-2 centers.

Accordingly, deprotection of the amine group by reduction of the sulfonamide of compound **18** under Na/Hg conditions afforded alcohol **20** in 83% yield. Reaction of ester **21** with alcohol **20** gave a 2:1 diastereomeric mixture of pyrrolo[1,2-*a*]indoles **19a,b** in 77% yield. Unfortunately in this reaction the diastereomers were formed with respect to the C-2 and C-3 centers and not at C-1 and C-2. The stereochemistry of diastereomers was unambiguously established by single-crystal X-ray analysis of the minor diastereomer **19b** and NOESY of the major diastereomer. The formation of diastereomers at C-2 and C-3 suggests that the reaction is not concerted but goes through a stepwise mechanism (Scheme 3). Interestingly treatment of the major diastereomer **19a** with an excess of MeMgI afforded the tertiary alcohol **22**, which on reaction with $BF_3 \cdot OEt_2$ generated the tetramethylpyran derivative **23** by attack of a hydroxyl oxygen at the C−C double bond. Screening of different Lewis acids did not generate either the ene reaction product or olefin cation cyclization product; instead, it gave a mixture of the three different compounds **23** and **24a,b** (Table 1). In our earlier synthesis of flinderoles,[9] we were surprised by the fact that the reaction of diene **25** with tertiary alcohol **26** under Lewis acid conditions generated only the [3 + 2] cycloaddition product **27** (Scheme 4), and we could not isolate even a trace of [4 + 2] cycloaddition product which could have led to the synthesis of borreverine (**7**) and isoborreverine (**5**). We began to wonder about the factor that made this reaction so selective. The diene **25** and tertiary alcohol **26** are structurally closely related to borrerine (**4**) and are analogous to a diene, which was shown as the intermediate in the borrerine dimerization to borreverine (**7**) and isoborreverine (**5**).[8] This made us reexamine the mechanism of the dimerization reaction. It was thought that an ethanol side chain at the 3-position of indole in diene **25** and tertiary alcohol **26** might play an important role to exclusively generate the [3 + 2] adduct. We became interested in dimerization of the tertiary alcohol **28**. Alcohol **28** could be synthesized from tryptophol **29** in two steps by bromination at the 2-position of tryptophol followed by coupling with an appropriate side chain. However, reaction of tryptophol **29** with NBS in refluxing CCl_4 generated bromoethylindole (**30**). To our delight, reaction of the methyl ester of indole acetic acid **31** with NBS in CCl_4 at room temperature afforded the bromination product **32** in 88% yield. Stille coupling of **32** with **33** afforded **34** in 77% yield. Reduction of the ester group in **34** using LAH generated the key intermediate **28** in 75% yield (Scheme 5). To our surprise,

Scheme 4. Synthesis of Compound 27



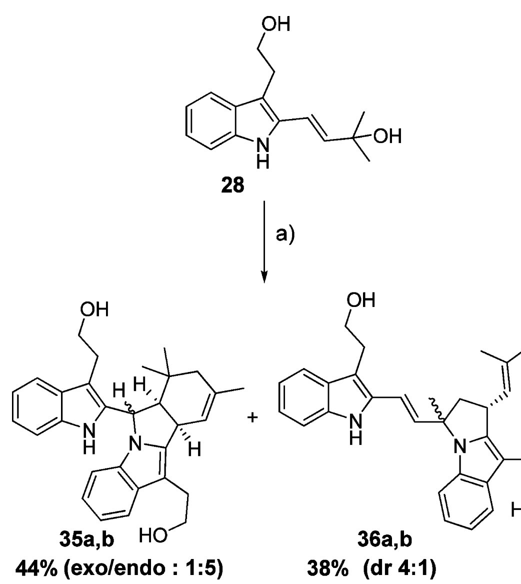
Scheme 5. Synthesis of Tertiary Alcohol 28[a]



[a]Legend: (a) NBS (1.1 equiv), CCl_4, reflux, 1 h, 67%; (b) **33** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), Bu_4NCl (2.0 equiv), DMF, reflux, 3 h, 77%; (c) $LiAlH_4$ (1.2 equiv), Et_2O, 0 °C to room temperature, 3 h, 75%.

dimerization of diol **28** using 10 mol % of $BF_3 \cdot OEt_2$ in CH_2Cl_2 generated both [4 + 2] and [3 + 2] cycloaddition products **35a,b** and **36a,b** with a combined yield of 82% in 5:1 and 4:1 diastereomeric ratios, respectively (Scheme 6). This was quite

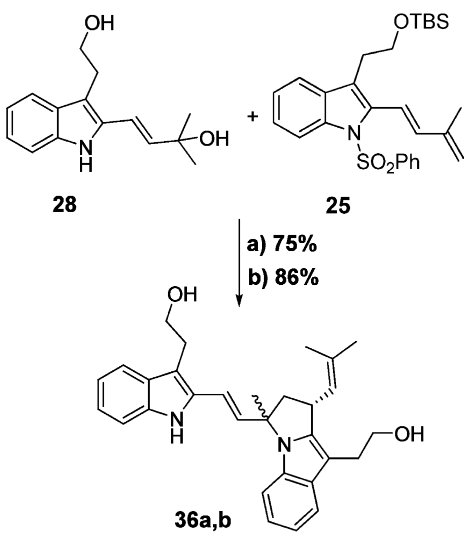
Scheme 6. Lewis Acid Catalyzed Dimerization of Tertiary Alcohol 28[a]



[a]Legend: (a) $BF_3 \cdot OEt_2$ (10 mol %), CH_2Cl_2, room temperature, 15 min, 82%.

interesting in the sense that, in our earlier synthesis of flinderoles,[9] tertiary alcohol **26** on reaction with diene **25** using $BF_3 \cdot OEt_2$ or $Cu(OTf)_2$ afforded only [3 + 2] product. All four compounds were separated by careful silica gel column chromatography, and their structures and stereochemistries were confirmed from their spectral data and comparison of spectral data of isoborreverine and flinderoles A–C. More interestingly, when a mixture of tertiary alcohol **28** and diene **25** was treated with Lewis acid, it generated only [3 + 2] cycloaddition product; no [4 + 2] product was observed in this reaction (Scheme 7). These results prompted us to propose a

Scheme 7. Intermolecular Formal [3 + 2] Cycloaddition Reaction[a]



[a]Legend: (a) $BF_3 \cdot OEt_2$ (0.1 equiv), CH_2Cl_2, room temperature, 10 min, 75%; (b) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, room temperature, 1 h, 86%.

mechanism for [3 + 2] and [4 + 2] cycloaddition different from that reported earlier by Koch et al. and later by our group. The tertiary alcohol **28** could first form the cyclic borrerine type intermediate **37**, which could then open in three different ways; depending on reaction conditions, compound **37** could be attacked by the indole nitrogen of another molecule of **37** (path A) to generate the intermediate **38** followed by an intramolecular Diels–Alder reaction leading to isoborreverine analogue **35**. On the other hand, compound **37** could first convert to diene **39** via intermediate **40** (path B or C), which then dimerizes itself or with compound **40** to afford the flinderole analogue **36** (Scheme 8). Intermediate **40** could also be generated directly from tertiary alcohol **28** by the push of the lone pair of indole nitrogen. If one uses a comparatively strong acid such as trifluoroacetic acid or $BF_3 \cdot OEt_2$, then path A becomes dominant as the carbon-bearing isobutenyl group becomes more electron deficient, which is also in line with our observation. Another important observation from Schemes 4 and 7 is that the moment diene **39** is present/formed in the reaction mixture, it undergoes a dimerization reaction with tertiary alcohol **28**/compound **37**/intermediate **40** to afford only [3 + 2] cycloaddition product, as the terminal double bond in diene **39** is more nucleophilic than indole nitrogen. This could also be justified from the fact that in May's synthesis of flinderole by dimerization of borrerine **4** using TFA, they only isolated isoborreverine (path A), but when they used acetic acid (a comparatively weak acid), they isolated flinderoles exclusively in excellent yield (path B). This mechanism could be further supported by the fact that reaction of tertiary alcohol **26** with diene **25** exclusively formed the [3 + 2] cycloaddition product **27** and no [4 + 2] cycloaddition was observed (Scheme 4). Oxidation of the diol **35a** using IBX followed by reductive amination of the resultant bis-aldehyde **41** using a 2 N THF solution of dimethylamine afforded dimethylisoborreverine (**6**) in 82% yield. However, reductive amination of the bis-aldehyde **41** using a 2 N THF solution of methylamine failed to generate isoborreverine (**5**) under various conditions. In our earlier synthesis of flinderoles as well, we faced same problems, because of which we failed to synthesize flinderole A (**1**). Fortunately, we came across a literature report[12] by Bandichhor et al. in which they reported that reductive amination of aldehyde using methylamine works very well in the presence of a catalytic amount of $Fe(OTf)_3$. To our delight, reductive amination of the bis-aldehyde **41** using a 2 N THF solution of methylamine in the presence of 30 mol % of $Fe(OTf)_3$ afforded isoborreverine (**5**) in 89% yield (Scheme 9). Similarly, independent oxidation of the diols **36a,b** by IBX followed by reductive amination of the resultant bis-aldehydes **42a,b** using a 2 N THF solution of dimethylamine afforded flinderoles B (**2**) and C (**3**), respectively, and reductive amination of the bis-aldehyde **42a** using a 2 N THF solution of methylamine in the presence of 30 mol % of $Fe(OTf)_3$ afforded flinderole A (**1**) in 75% yield (Scheme 10).

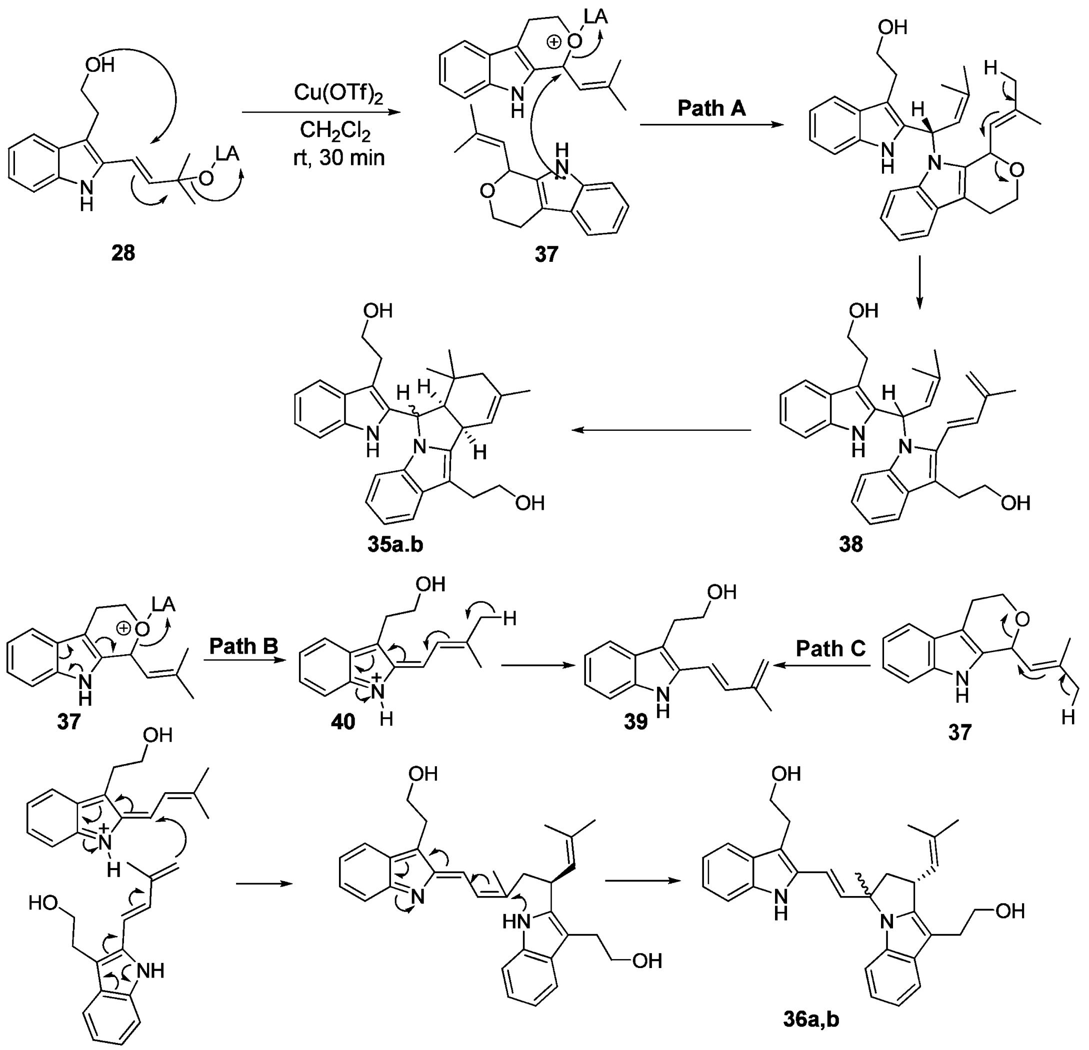
Thus, we completed the synthesis of flinderoles A (**1**), B (**2**), and C (**3**), isoborreverine (**5**) and dimethylisoborreverine (**6**) in just six steps starting from tryptophol **29** using a protecting-group-free approach. We also made diene **43**, to check whether it is an actual intermediate in the dimerization of borrerine (**4**) to isoborreverine (**5**) as proposed by Koch et al. in their mechanism.[8] Tryptamine **44** on treatment with $ClCO_2Et$ followed by protection of the indole nitrogen using $PhSO_2Cl$ afforded compound **45** in 91% yield. Formylation of **45** followed by a Wittig reaction of the resultant aldehyde **46** and treatment of ester **47** thus generated with MeMgI afforded the tertiary alcohol **48** in 75% yield.

Mesylation followed by elimination afforded the diene **49**. Deprotection of the amine group by reduction of the sulfonamide of compound **49** using Na/Hg followed by $LiAlH_4$ reduction of the resultant indole derivative **50** afforded diene **43** in 66% yield (Scheme 11). Diene **43** on treatment with trifluoroacetic acid afforded isoborreverine (**5**) but only in 20% yield; in contrast to previous reports[8] we did not observe the formation of borreverine (**7**). May et al. also obtained similar results in the dimerization of borrerine (**4**) using trifluoroacetic acid with 90% yield of isoborreverine (**5**).[11] Interestingly, however, alcohol **51** generated from **48** by a deprotection–reduction sequence on treatment with CF_3CO_2H in CH_2Cl_2 furnished isoborreverine (**5**) in 86% yield (Scheme 12).

■ CONCLUSIONS

The chemistry described herein demonstrates the power of cycloaddition reactions in complex molecule construction and provides access to flinderoles A (**1**), B (**2**), and C (**3**), isoborreverine (**5**) and dimethylisoborreverine (**6**), two different classes of structurally intriguing and highly potent antimalarial natural products. A detailed study of the dimerization reaction caused us to propose a mechanism for dimerization of tertiary alcohol **32** slightly different from the

Scheme 8. Proposed Mechanism for the Dimerization of Tertiary Alcohol 28



earlier reported dimerization of borrerine. The preparation and dimerization of diene **10** also supported the proposed biosynthetic pathway.

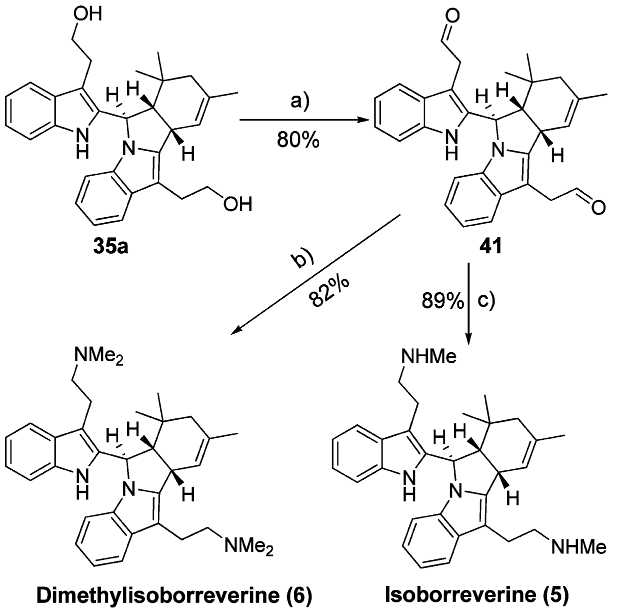
■ EXPERIMENTAL SECTION

General Aspects. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise mentioned. All of the chemicals were purchased commercially and used without further purification. Anhydrous THF and diethyl ether were distilled from sodium benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically pure compounds, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and an *p*-anisaldehyde or ninhydrine stain and heat as developing agents. Merck silica gel (particle size 100−200 and 230−400 mesh) was used for flash column chromatography. Neat coupounds were used for recording IR spectra. NMR spectra were recorded on a Bruker Avance 200 (^{1}H, 200 MHz; ^{13}C, 50 MHz), Bruker Avance 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Bruker Avance 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz), or JEOL DELTA (ECX) 500 instrument (^{1}H, 500 MHz; ^{13}C, 125 MHz). Mass spectrometric data were obtained using WATERS-Q-Tof-Premier-HAB213 and WATERS-Q-Tof-Premier-ESI-MS instruments. Melting point measurements were made using a hot stage apparatus. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, br = broad.

Experimental Procedures. *3-Methyl-1-(3-methyl-1-(phenylsulfonyl)-1H-indol-2-yl)but-3-en-1-ol (**18**).* To a magnetically stirred solution of magnesium turnings (243 mg, 10.03 mmol) and a few crystals of iodine in anhydrous THF (10 mL) was added a mixture of aldehyde **17** (2.0 g, 6.68 mmol) and 3-chloro-2-methylprop-1-ene (0.97 mL, 10.03 mmol) in THF (20 mL) dropwise with gentle heating, and this mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with aqueous NH_4Cl solution (20 mL) and worked up. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1.5/8.5) as eluent furnished the alcohol **18** (2.0 g, 84%) as a yellowish semisolid: R_f = 0.5 (EtOAc/hexane 1/4); IR (neat) ν_{max}/cm^{-1} 3547, 2919, 1448, 1364, 1170, 1151, 740, 594, 576; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (br d, J = 8.2 Hz, 1H), 7.78 (br d, J = 7.3 Hz, 2H), 7.44 (td, J = 7.6, 7.3 Hz, 1H), 7.39 (dd, J = 7.69, 7.0 Hz, 1H), 7.33 (br t, J = 8.2, Hz, 2H), 7.27 (td, J = 7.3, 1.2 Hz, 1H), 7.22 (td, J = 7.6, 7.3 Hz, 1H), 5.46 (br s, 1H), 4.84 (s, 2H), 3.52 (br s, 1H), 2.87 (dd, J = 8.5, 4.5 Hz, 1H), 2.71 (dd, J = 7.9, 5.8 Hz, 1H), 2.31 (s, 3H), 1.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.9 (C), 137.9 (C), 137.5 (C), 136.6 (C), 133.6 (CH), 131.3 (C), 128.9 (2 CH), 126.3 (2 CH), 125.2 (CH), 123.7 (CH), 120.3 (C), 119.1 (CH), 115.1 (CH), 113.7 (CH_2), 65.7 (CH), 45.5 (CH_2), 22.1 (CH_3), 9.7 (CH_3); HRMS m/z calcd for $C_{20}H_{21}NO_3S$ [M + Na^{+}] 378.1140, found 378.1142.

*3-Methyl-1-(3-methyl-1-(phenylsulfonyl)-1H-indol-2-yl)but-3-en-1-one (**18a**).* To a solution of the alcohol **18** (1.5 g, 4.24 mmol) in ethyl acetate (25 mL) was added IBX (7.1 g, 25.5 mmol), and the

Scheme 9. Completion of Total Synthesis of Isoborreverine 5 and Dimethylisoborreverine 6[a]

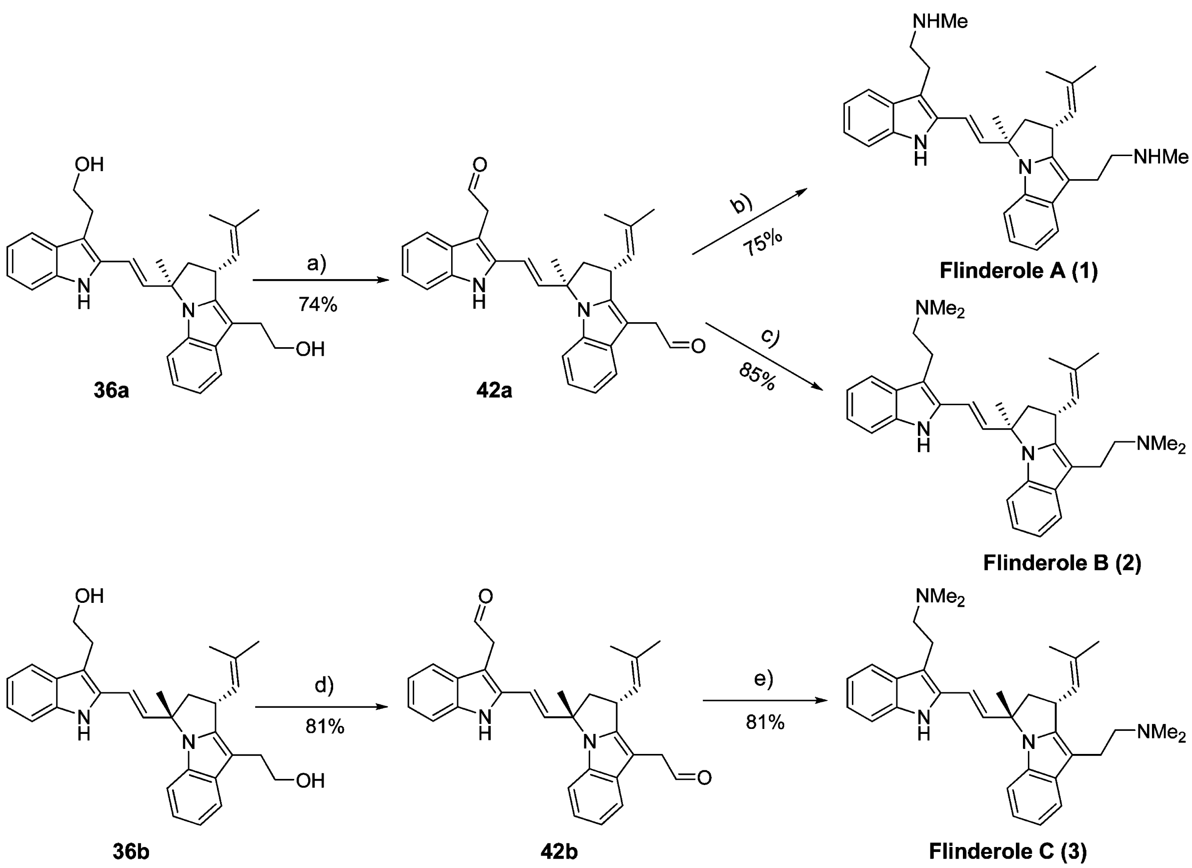


[a]Legend: (a) IBX (4.0 equiv), EtOAc, reflux, 1 h, 80%; (b) $NHMe_2$ (4.0 equiv), $NaCNBH_3$ (4.0 equiv), AcOH (cat.), MeOH, room temperature, 12 h, 82%; (c) NH_2Me (5.0 equiv), $NaBH_4$ (5.0 equiv), $Fe(OTf)_3$ (0.3 equiv), CH_2Cl_2, room temperature, 30 min, 89%.

mixture was refluxed for 3 h. Aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 20 mL). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/9) as eluent furnished compound **18a** (1.2 g, 80%) as a waxy solid: R_f = 0.6 (EtOAc/hexane 1.5/8.5); IR (neat) ν_{max}/cm^{-1} 3316, 2917, 1679 (C═O), 1446, 1365, 1175, 946, 743, 594, 572; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 7.8 Hz, 2H), 7.42−7.23 (m, 6H), 4.90 (s, 1H), 4.82 (s, 1H), 3.79 (s, 2H), 2.19 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.5 (C═O), 138.9 (C), 137.1 (C), 135.7 (C), 134.9 (C), 133.8 (CH), 131.7 (C), 128.6 (2 CH), 127.3 (CH), 127.2 (2 CH), 127.1 (C), 124.8 (CH), 120.7 (CH), 116.0 (CH), 115.2 (CH_2), 53.2 (CH_2), 22.6 (CH_3), 9.3 (CH_3); HRMS m/z calcd for $C_{20}H_{19}NO_3S$ [M + H$^+$] 354.1186, found 354.1160.

*3-Methyl-1-(3-methyl-1-(phenylsulfonyl)-1H-indol-2-yl)but-2-en-1-one (**15**).* To a magnetically stirred solution of the alcohol **18a** (500 mg, 1.41 mmol) in anhydrous CH_2Cl_2 (10 mL) was added DBU (0.2 mL, 1.41 mmol) in a dropwise fashion, and the mixture was stirred for 1 h at room temperature. The progress of the reaction was monitored by TLC until the starting alcohol had been completely consumed. Water (5 mL) was then added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (5 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/9) as eluent furnished compound **15** (450 mg, 90%) as a yellowish solid: R_f = 0.4 (EtOAc/hexane 1/4); mp 79−81 °C; IR (neat) ν_{max}/cm^{-1} 2940, 1666 (C═O), 1612, 1445, 1366, 1182, 945, 862, 772, 577; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 7.5 Hz, 2H), 7.43−7.22 (m, 6H), 6.56 (s, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 1.98 (s,

Scheme 10. Completion of Total Synthesis of Flinderoles A−C[a]



[a]Legend: (a) IBX (4.0 equiv), EtOAc, reflux, 1 h, 74%; (b) NH_2Me (5.0 equiv), $NaBH_4$ (5.0 equiv), Fe $(OTf)_3$ (0.3 equiv), CH_2Cl_2, room temperature, 30 min, 75%; (c), $NHMe_2$ (4.0 equiv), $NaCNBH_3$ (4.0 equiv), AcOH (cat.), MeOH, room temperature, 12 h, 85%; (d) IBX (4.0 equiv), EtOAc, reflux, 1 h, 81%; (e) $NHMe_2$ (4.0 equiv), $NaCNBH_3$ (4.0 equiv), AcOH (cat.), MeOH, room temperature, 12 h, 81%;

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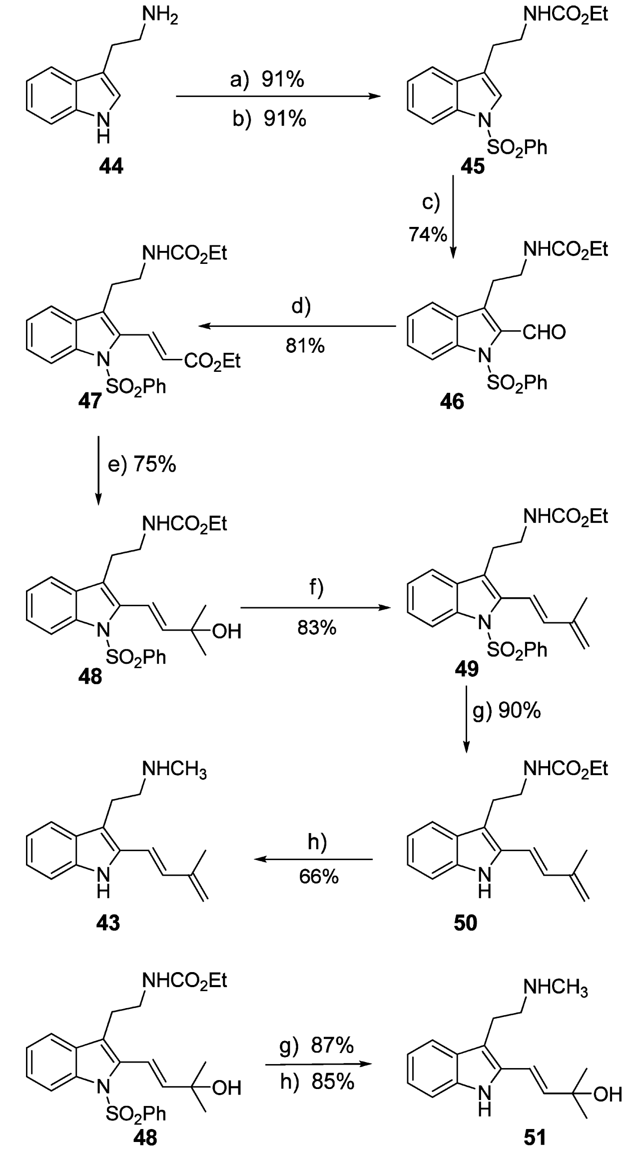
Scheme 11. Synthesis of Tertiary Alcohol 51 and Diene 43[a]

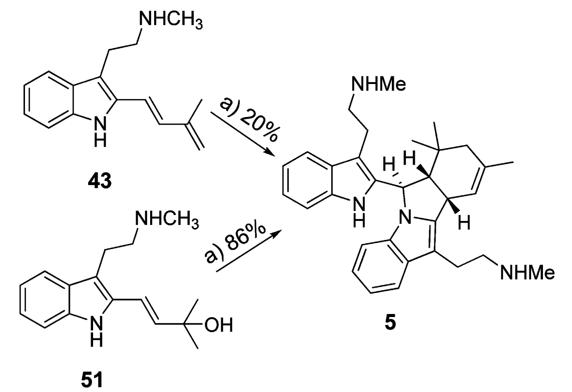


[a]Legend: (a) $NaHCO_3$ (1.5 equiv), NaCl (4.4 equiv), $ClCO_2Et$ (1.5 equiv), CH_2Cl_2, H_2O, room temperature, 3 h, 91%; (b) KOH (5.0 equiv), $PhSO_2Cl$ (3.0 equiv), THF, room temperature, 6 h, 91%; (c) Cl_2CHOCH_3 (5.0 equiv), $SnCl_4$ (5.0 equiv), CH_2Cl_2, −78 to −10 °C, 1 h, 74%; (d) $Ph_3P{=}CHCO_2Et$ (2.0 equiv), CH_2Cl_2, room temperature, 6 h, 81%; (e) MeI (6.0 equiv), Mg turnings (5.0 equiv), I_2 (cat.), Et_2O, 0 °C to room temperature, 2 h, 75%; (f) MsCl (3.0 equiv), Et_3N (6.0 equiv), THF, 0 °C to room temperature and reflux, 2 h, 83%; (g) Na/Hg (5.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, room temperature, 1 h, 90%; (h) $LiAlH_4$ (1.0 M solution) (5.0 equiv), THF, room temperature, 3 h, 66%.

3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 186.8 (C═O), 155.6 (C), 137.2 (C), 136.8 (C), 135.9 (C), 133.6 (CH), 131.7 (C), 128.6 (2 CH), 127.1 (2 CH), 126.8 (CH), 125.9 (CH), 125.6 (C), 124.4 (CH), 120.4 (CH), 115.8 (C), 27.9 (CH_3), 21.0 (CH_3), 9.3 (CH_3); HRMS *m/z* calcd for $C_{20}H_{19}NO_3S$ [M + H$^+$] 354.1186, found 354.1167.

*3-Methyl-1-(3-methyl-1H-indol-2-yl)but-3-en-1-ol (**20**).* To a solution of the alcohol **18** (2 g, 5.63 mmol) in anhydrous methanol (30 mL) was added Na_2HPO_4 (3.2 g, 22.53 mmol) and Na−Hg (5.0 g, 22.53 mmol). The reaction mixture was stirred for 1 h at room temperature. Water (10 mL) and ether (20 mL) were added, and the supernatant was decanted. The residue was washed with ether (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (2/8) as eluent gave the alcohol **20** (1.0 g, 83%) as a yellow waxy solid: R_f = 0.4 (EtOAc/hexane 1.5/8.5); IR (neat) ν_{max}/cm^{-1} 3406, 2918, 1647, 1526, 1451, 1335, 1306, 894, 742; ^{1}H NMR (CD_3CN, 400 MHz) δ 6.63 (dt, *J* = 6.6, 1.2 Hz, 1H), 6.50 (dt, *J* = 6.3, 1.7 Hz, 1H), 6.26 (ddd, *J* = 7.1, 5.8, 1.2 Hz, 1H), 6.18 (ddd, *J* = 7.1, 6.0, 1.2 Hz, 1H), 4.28 (t, *J* = 7.5 Hz, 1H), 3.92−3.88 (br d, 2H), 1.70, (m, 2H), 1.41 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 143.5 (C), 138.0 (C), 136.6 (C), 129.9 (C), 122.2 (CH), 119.6 (CH), 119.2 (CH), 113.6 (CH_2), 111.8 (CH), 107.1 (C), 65.4 (CH), 46.4 (CH_2), 22.7 (CH_3), 8.7 (CH_3); HRMS *m/z* calcd for $C_{14}H_{17}NO$ [M + H − H_2O^+] 198.1304, found 198.1283.

Scheme 12. Dimerization of Diene 43 and Tertiary Alcohol 51[a]



[a]Legend: (a) CF_3CO_2H (0.5 equiv), CH_2Cl_2, room temperature, 30 min.

*(3-Methyl-1-(phenylsulfonyl)-1H-indol-2-yl)methanol (**21a**).* To a solution of the aldehyde **17** (4.0 g, 13.37 mmol) in anhydrous THF (40 mL) was added $LiAlH_4$ (2.47 g, 66.88 mmol) at 0 °C. The mixture was stirred for 1 h and quenched with a saturated solution of NH_4Cl and extracted with EtOAc; the organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (7.5/2.5) as eluent gave the alcohol **21a** (3.3 g, 82%) as a white waxy oil: R_f = 0.5 (EtOAc/hexane 7/3); IR (neat) ν_{max}/cm^{-1} 3593, 3423 (OH), 1450, 1361, 1172, 997, 751, 685, 560; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.83 (br d, *J* = 9.5 Hz, 2H), 7.54−7.27 (m, 6H), 4.92 (s, 2H), 3.29 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.4 (C), 136.0 (C), 134.9 (C), 133.7 (CH), 130.6 (C), 129.2 (2 CH), 126.2 (2 CH), 125.4 (CH), 123.6 (CH), 119.5 (CH), 119.4 (C), 114.4 (CH), 54.9 (CH_2), 8.9 (CH_3); HRMS *m/z* calcd for $C_{16}H_{15}NO_3S$ [M + NH_4^+] 319.1100, found 319.1118, and [M + Na$^+$] 324.0700, found 324.0671.

*(3-Methyl-1H-indol-2-yl)methanol (**21b**).* To a solution of the alcohol **21a** (3.0 g, 9.96 mmol) in anhydrous methanol (30 mL) was added Na_2HPO_4 (5.6 g, 39.86 mmol) and Na−Hg (8.9 g, 39.86 mmol). The reaction mixture was stirred for 1 h at room temperature. Water (15 mL) and ether (20 mL) were added, and the supernatant was decanted. The residue was washed with ether (3 × 15 mL). The organic extracts were combined, washed with brine (15 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1/4) as eluent gave the alcohol **21b** (1.3 g, 81%) as a yellow semisolid; R_f = 0.4 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3401, 2921, 1622, 1459, 1333, 1242, 743; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (br s, 1H), 7.53 (br d, *J* = 7.4 Hz, 1H), 7.30−7.06 (m, 3H), 4.76 (s, 2H), 2.27 (s, 3H), 1.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.6 (C), 132.8 (C), 128.7 (C), 122.2 (CH), 119.2 (CH), 118.8 (CH), 110.7 (CH), 108.4 (C), 56.5 (CH_2), 8.3 (CH_3); HRMS *m/z* calcd for $C_{10}H_{11}NO$ [M + H$^+$] 162.0900, found 162.0914.

*3-Methyl-1H-indole-2-carbaldehyde (**21c**).* To a solution of the alcohol **21b** (1.2 g, 7.40 mmol) in ethyl acetate (10 mL) was added

IBX (8.2 g, 29.62 mmol), and the mixture was refluxed for 1 h. Aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/9) as eluent furnished the aldehyde **21c** (1.0 g, 84%) as a white semisolid: R_f = 0.6 (EtOAc/hexane 1.5/8.5); IR (neat) ν_{max}/cm^{-1} 3308, 2849, 1637 (C=O), 1574, 1460, 1232, 1114, 873, 741, 613; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.04 (s, 1H), 9.15 (br s, 1H), 7.70 (br d, *J* = 8.2 Hz, 1H), 7.41−7.36 (m, 2H), 7.17−7.13 (m, 1H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 180.6 (CHO), 137.6 (C), 132.1 (C), 128.1 (C), 127.6 (CH), 125.1 (C), 121.3 (CH), 120.3 (CH), 112.3 (CH), 8.3 (CH_3); HRMS *m/z* calcd for $C_{10}H_9NO$ [M + H$^+$] 160.0800, found 160.0766.

(E)-Ethyl 3-(3-Methyl-1H-indol-2-yl)acrylate (21). To a solution of the aldehyde **21c** (1.0 g, 6.25 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dry $Ph_3P{=}CHCO_2Et$ (4.3 g, 12.5 mmol), and the mixture was stirred magnetically for 6 h at room temperature. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1/9) as eluent gave the ester **21** (1.3 g, 90%) as a white crystalline solid: R_f = 0.45 (EtOAc/hexane 1.5/8.5); mp 163−165 °C; IR (neat) ν_{max}/cm^{-1} 3326 (NH), 1684 (OC=O), 1612, 1295, 961, 730, 586; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 (br s, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.56 (br d, *J* = 7.9 Hz, 1H), 7.33−7.06 (m, 3H), 6.18 (d, *J* = 16.0 Hz, 1H), 4.30 (q, *J* = 7.2, 7.0 Hz, 2H), 2.40 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4 (OC=O), 137.4 (C), 132.3 (CH), 129.9 (C), 128.9 (C), 124.9 (CH), 119.8 (2 CH), 118.6 (C), 113.7 (CH), 110.9 (CH), 60.5 (CH_2), 14.3 (CH_3), 8.8 (CH_3); HRMS *m/z* calcd for $C_{14}H_{15}NO_2$ [M + H$^+$] 230.1203, found 230.1185.

(1S,2S,3S)-Ethyl 9-Methyl-3-(3-methyl-1H-indol-2-yl)-1-(2-methylallyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-2-carboxylate (19a) and (1S,2S,3R)-Ethyl 9-Methyl-3-(3-methyl-1H-indol-2-yl)-1-(2-methylallyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-2-carboxylate (19b). **19a**: to a solution of the alcohol **20** (300 mg, 1.39 mmol) and ester **21** (385 mg, 1.67 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a catalytic amount of $BF_3{\cdot}OEt_2$ (39 mg, 0.27 mmol). The resulting purplish red solution was stirred for 5 min at room temperature. Aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (0.6/9.4) as eluent furnished the major isomer **19a** (340 mg, 52%) as a white semisolid: R_f = 0.45 (EtOAc/hexane 1/9); IR (neat) ν_{max}/cm^{-1} 3387, 2922, 1730 (OC=O), 1457, 1373, 1301, 1029, 742; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (br s, 1H), 7.59 (br d, *J* = 7.0 Hz, 1H), 7.50 (br d, *J* = 8.0 Hz, 1H), 7.14−7.10 (m, 3H), 7.04 (br t, *J* = 8.0, 7.0 Hz, 1H), 6.87 (br t, *J* = 8.0, 7.2 Hz, 1H), 6.63 (br d, *J* = 8.0 Hz, 1H), 5.81 (d, *J* = 7.2 Hz, 1H), 4.84 (br s, 1H), 4.73 (br s, 1H), 4.24−4.09 (m, 2H), 3.96 (br m, 1H), 3.52 (t, *J* = 7.0 Hz, 1H), 2.87 (dd, *J* = 9.2, 4.5 Hz, 1H), 2.51 (dd, *J* = 9.0, 4.7 Hz, 1H), 2.35 (s, 6H), 1.80 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.4 (OC=O), 142.5 (C), 141.8 (C), 135.9 (C), 134.1 (C), 132.5 (C), 131.3 (C), 129.3 (C), 122.4 (CH), 121.1 (CH), 119.5 (2 CH), 118.9 (CH), 118.5 (CH), 114.4 (CH_2), 111.1 (CH), 110.0 (C), 109.9 (CH), 102.5 (C), 61.5 (CH_2), 60.2 (CH), 55.9 (CH), 42.2 (CH_2), 39.2 (CH), 22.6 (CH_3), 14.2 (CH_3), 8.8 (CH_3), 8.5 (CH_3); HRMS *m/z* calcd for $C_{28}H_{30}N_2O_2$ [M + H$^+$] 427.2407, found 427.2383.

19b: further elution of the column with EtOAc/hexane (1.5/8.5) gave the minor isomer **19b** (165 mg, 25%) as a yellow crystalline solid: R_f = 0.4 (EtOAc/hexane 1/9); mp 105−107 °C; IR (neat) ν_{max}/cm^{-1} 3386, 2918, 1731, 1458, 1370, 1302, 1188, 1031, 739; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (br t, *J* = 7.7, 6.2 Hz, 2H), 7.44 (br s, 1H), 7.09−7.02 (m, 4H), 6.92 (br t, *J* = 7.7, 7.2 Hz, 1H), 6.72 (br d, *J* = 8.2 Hz, 1H), 6.06 (d, *J* = 8.7 Hz, 1H), 4.83 (br d, 2H), 4.20−4.15 (m, 1H), 3.84 (dd, *J* = 6.0, 2.7 Hz, 1H), 3.79−3.73 (m, 1H), 3.64−3.58 (m, 1H), 2.85 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.39 (s, 6H), 2.35 (br d, 1H), 1.79 (s, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (OC=O), 142.8 (C), 141.7 (C), 135.6 (C), 133.9 (C), 131.8 (C), 128.9 (C), 128.6 (C), 122.2 (CH), 121.0 (CH), 119.3 (CH), 119.1 (CH), 118.5 (CH), 118.4 (CH), 113.6 (CH_2), 110.9 (CH), 110.3 (C), 109.7 (CH), 102.3 (C), 61.0 (CH_2), 58.1 (CH), 53.8 (CH), 42.0 (CH_2), 37.1 (CH), 22.2 (CH_3), 13.5 (CH_3), 8.8 (CH_3), 8.5 (CH_3); HRMS *m/z* calcd for $C_{28}H_{30}N_2O_2$ [M + H$^+$] 427.2407, found 427.2386.

2-((1S,2R,3S)-9-Methyl-3-(3-methyl-1H-indol-2-yl)-1-(2-methylallyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl)propan-2-ol (22). To a cold (0 °C), magnetically stirred solution of the major isomer ester **19a** (500 mg, 1.16 mmol) in anhydrous ether (10 mL) was added methylmagnesium iodide (prepared from magnesium turnings (170 mg, 7.00 mmol), methyl iodide (0.5 mL, 8.17 mmol), and a few crystals of iodine in anhydrous ether (10 mL)), and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with aqueous NH_4Cl solution (50 mL) and worked up. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (2.5/7.5) as eluent furnished the tertiary alcohol **22** (410 mg, 85%) as a white semisolid: R_f = 0.4 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3397, 2971, 2924, 1459, 1373, 1240, 740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (br s, 1H), 7.55−7.49 (m, 2H), 7.16−7.02 (m, 4H), 6.98−6.89 (m, 2H), 5.67 (d, *J* = 3.3 Hz, 1H), 4.86 (s, 1H), 4.61 (s, 1H), 3.39−3.35 (m, 1H), 2.83 (t, *J* = 3.1 Hz, 1H), 2.57 (dd, *J* = 7.7, 5.5 Hz, 1H), 2.45 (dd, *J* = 8.1, 5.1 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.4 (C), 143.3 (C), 135.6 (C), 134.1 (C), 133.6 (C), 132.1 (C), 129.4 (C), 121.9 (CH), 120.6 (CH), 119.1 (2 CH), 118.5 (CH), 118.3 (CH), 114.7 (CH_2), 110.7 (CH), 109.7 (CH), 107.8 (C), 101.3 (C), 72.5 (C), 66.4 (CH), 54.0 (CH), 44.5 (CH_2), 37.3 (CH), 28.1 (CH_3), 25.9 (CH_3), 22.6 (CH_3), 8.9 (CH_3), 8.5 (CH_3); HRMS *m/z* calcd for $C_{28}H_{32}N_2O$ [M + H$^+$] 413.2615, found 413.2594.

(6S,6aS,10aS)-7,7,9,9,11-Pentamethyl-6-(3-methyl-1H-indol-2-yl)-6a,7,8,9,10,10a-hexahydro-8-oxa-isoindolo[2,1-a]indole (23). To a solution of the tertiary alcohol **22** (70 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (24 mg, 0.17 mmol). The resulting purplish red solution was stirred for 16 h at room temperature. Aqueous $NaHCO_3$ (5 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (0.5/9.5) as eluent furnished compound **23** (50 mg, 71%) as a white semisolid: R_f = 0.5 (EtOAc/hexane 1/9) (in a similar fashion PTSA (1.69 mmol), CH_2Cl_2 (5 mL), room temperature, and 24 h gave 70% yield, PTSA (0.84 mmol), benzene (5 mL), 80 °C, and 2 h gave 62% yield, and triflic acid (0.16 mmol), CH_2Cl_2 (5 mL), room temperature, and 30 min gave 70% yield): IR (neat) ν_{max}/cm^{-1} 3392, 2973, 2929, 1458, 1380, 1331, 1296, 1164, 976, 740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (br s, 1H), 7.63−7.61 (m, 1H), 7.47 (dd, *J* = 7.7 Hz, 1H), 7.17−7.13 (m, 3H), 6.97 (br t, *J* = 7.3 Hz, 1H), 6.78 (br t, *J* = 7.3 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 3.51 (br t, *J* = 12.0 Hz, 1H), 2.52 (dd, *J* = 9.2, 3.2 Hz, 2H), 2.47 (s, 3H), 2.34 (s, 3H), 1.80 (br t, *J* = 12.5 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.4 (C), 136.1 (C), 132.6 (C), 132.5 (C), 130.4 (C), 128.6 (C), 122.5 (CH), 121.0 (CH), 119.3 (CH), 118.8 (CH), 118.7 (CH), 118.2 (CH), 111.0 (CH), 110.9 (C), 109.1 (CH), 102.1 (C), 73.9 (C), 72.7 (C), 64.9 (CH), 54.6 (CH), 40.8 (CH_2), 33.9 (CH), 33.4 (CH_3), 31.0 (CH_3), 28.3 (CH_3), 24.0 (CH_3), 8.7 (CH_3), 8.4 (CH_3); HRMS *m/z* calcd for $C_{28}H_{32}N_2O$ [M + H$^+$] 413.2615, found 413.2590.

(1S,2R,3S)-9-Methyl-3-(3-methyl-1H-indol-2-yl)-1-(2-methylallyl)-2-(prop-1-en-2-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole (24a). To a solution of the tertiary alcohol **22** (200 mg, 0.48 mmol) in anhydrous THF (8 mL) and Et_3N (0.4 mL, 2.91 mmol) under an N_2 atmosphere was added MsCl (0.1 mL, 1.45 mmol) slowly over a period of 5 min at 0 °C. The solution was warmed to room temperature for about 1.5 h and then refluxed for 30 min. The precipitate that formed was filtered off using ethyl acetate, affording a brown viscous liquid. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/9) as eluent furnished compound **24a** (118 mg, 62%) as a colorless waxy solid: R_f = 0.5 (EtOAc/hexane 1/9); IR (neat) ν_{max}/cm^{-1} 3394, 2918, 1459, 1373, 1301, 894, 741; ^{1}H NMR

($CDCl_3$, 200 MHz) δ 7.69 (br s, 1H), 7.60−7.49 (m, 2H), 7.17−7.09 (m, 3H), 7.03 (dd, J = 6.8, 1.1 Hz, 1H), 6.89 (td, J = 7.0, 1.1 Hz, 1H), 6.64 (dt, J = 8.0, 1.1 Hz, 1H), 5.39 (d, J = 6.9, 1H), 4.87 (t, J = 7.5 Hz, 1H), 4.82−4.78 (m, 2H), 4.71 (br s, 1H), 3.53 (q, J = 6.9, 5.5 Hz, 1H), 3.31 (t, J = 6.9 Hz, 1H), 2.72 (dd, J = 8.9, 5.3 Hz, 1H), 2.45 (dd, J = 7.8, 6.4 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 1.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.3 (C), 143.0 (C), 142.8 (C), 135.6 (C), 133.8 (C), 132.4 (2 C), 129.3 (C), 121.9 (CH), 120.8 (CH), 119.2 (2 CH), 118.6 (CH), 118.3 (CH), 114.5 (CH_2), 113.6 (CH_2), 110.9 (CH), 109.8 (CH), 109.4 (C), 102.2 (C), 64.0 (CH), 57.2 (CH), 42.0 (CH_2), 39.0 (CH), 22.6 (CH_3), 19.5 (CH_3), 8.9 (CH_3), 8.6 (CH_3); HRMS m/z calcd for $C_{28}H_{30}N_2$ [M + H$^+$] 395.2509, found 395.2484.

*2-((1S,2S,3S)-9-Methyl-3-(3-methyl-1H-indol-2-yl)-1-(2-methylprop-1-enyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl)propan-2-ol (**24b**).* To a solution of the tertiary alcohol **22** (70 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $TiCl_4$ (93 mg, 0.84 mmol). The resulting purplish red solution was stirred for 4 h at room temperature. Aqueous $NaHCO_3$ (5 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1/3) as eluent furnished compound **24b** (40 mg, 57%) as a yellow waxy oil: R_f = 0.5 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3383, 2971, 2925, 1710, 1456, 1374, 1248, 742; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (br s, 1H), 7.57 (br d, J = 4.5, 1.7 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.19−7.09 (m, 3H), 6.98 (br t, J = 7.0 Hz, 1H), 6.83 (br t, J = 7.0 Hz, 1H), 6.62 (br d, J = 8.0 Hz, 1H), 5.65 (d, J = 6.5 Hz, 1H), 5.33 (br d, J = 10.0 Hz, 1H), 4.16 (dd, J = 6.7, 3.2 Hz, 1H), 2.87 (t, J = 6.5 Hz, 1H), 2.35 (s, 3H), 2.18 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H), 1.26−1.25 (d, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 141.4, 135.9, 133.5, 133.4, 132.0, 131.9, 129.1, 126.0, 122.2, 120.6, 119.2, 118.9, 118.7, 118.1, 110.9, 109.5, 109.4, 101.8, 72.4 (CH), 68.3 (CH), 53.9 (C), 38.4 (CH), 29.0 (CH_3), 27.1 (CH_3), 25.7 (CH_3), 18.3 (CH_3), 8.7 (CH_3), 7.7 (CH_3); HRMS m/z calcd for $C_{28}H_{32}N_2O$ [M + H$^+$] 413.2615, found 413.2592.

*3-(2-Bromoethyl)-1H-indole (**30**).* To a stirred solution of the tryptophol **29** (250 mg, 1.55 mmol) in anhydrous CCl_4 (10 mL) was added freshly recrystallized NBS (N-bromosuccinimide; 304 mg, 1.70 mmol) in 100 mg portions. The mixture was refluxed for 1 h and filtered, and the filtrate was concentrated under reduced pressure. Purification of the residue on a silica gel column using EtOAc/hexane (1.5/8.5) as eluent gave the bromoethylindole **30** (230 mg, 67%) as a yellow semisolid: R_f = 0.5 (EtOAc/hexane 1/4); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.52 (br d, J = 7.8 Hz, 1H), 7.29 (br d, J = 8.0 Hz, 1H), 7.14 (br t, J = 8.0 Hz, 1H), 7.07 (br t, J = 7.7 Hz, 1H), 7.00 (br d, J = 2.0 Hz, 1H), 3.56 (t, J = 7.7 Hz, 2H), 3.26 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.1 (C), 126.9 (C), 122.2 (2 CH), 119.6 (CH), 118.4 (CH), 113.5 (C), 111.3 (CH), 32.9 (CH_2), 29.3 (CH_2).

*Methyl 2-(1H-Indol-3-yl)acetate (**31**).* To a magnetically stirred solution of the indole 3-acetic acid **31a** (10 g, 57.14 mmol) in MeOH (250 mL) was added concentrated H_2SO_4 (1.5 mL, 28.57 mmol) dropwise at room temperature; the mixture was stirred for 1 h. The MeOH was evaporated, a saturated solution of $NaHCO_3$ was added, and this mixture was extracted with CH_2Cl_2. The organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (2/8) as eluent gave the ester **31** (10 g, 92%) as a white semisolid; R_f = 0.45 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3410 (NH), 3057, 2952, 1731 (OC═O), 1457, 1338, 1166, 1010, 743, 584; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.25 (br s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.29−7.20 (m, 3H), 6.98 (s, 1H), 3.85 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (OC═O), 135.9 (C), 126.9 (C), 123.2 (CH), 121.8 (CH), 119.3 (CH), 118.5 (CH), 111.2 (CH), 107.6 (C), 51.8 (CH_3), 30.9 (CH_2); HRMS m/z calcd for $C_{11}H_{11}NO_2$ [M + H$^+$] 190.0900, found 190.0867.

*Methyl 2-(2-Bromo-1H-indol-3-yl)acetate (**32**).* To a solution of the ester **31** (10 g, 52.91 mmol) in anhydrous CCl_4 (200 mL) was added freshly recrystallized NBS (N-bromosuccinimide; 10.3 g, 58.21 mmol) in 1 g portions. The mixture was stirred at room temperature for 1 h and was concentrated under reduced pressure. The purification of the residue on a silica gel column using EtOAc/hexane (1.5/8.5) as eluent gave the 2-bromo ester **32** (12.4 g, 88%) as a yellow waxy oil: R_f = 0.4 (EtOAc/hexane 1/4); IR (neat) ν_{max}/cm^{-1} 3335 (NH), 2951, 2850, 1728 (OC═O), 1435, 1336, 1202, 1167, 1013, 742, 628; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.46 (br s, 1H), 7.55−7.52 (m, 1H), 7.17−7.10 (m, 3H), 3.78 (s, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8 (OC═O), 135.9 (C), 127.2 (C), 122.2 (CH), 120.1 (CH), 118.0 (CH), 110.6 (CH), 109.7 (C), 108.0 (C), 50.1 (CH_3), 30.7 (CH_2); HRMS m/z calcd for $C_{11}H_{10}BrNO_2$ [M + H$^+$] 268.0000, found 267.9975.

*(E)-Methyl 2-(2-(3-Hydroxy-3-methylbut-1-enyl)-1H-indol-3-yl)-acetate (**34**).* To a solution of the 2-bromoindole ester **36** (400 mg, 1.42 mmol) in anhydrous DMF (6 mL) was added freshly prepared (E)-2-methyl-4-(tributylstannyl)but-3-en-2-ol (**37**; 802 mg, 2.13 mmol) subsequently followed by $Pd(OAc)_2$ (48 mg, 0.21 mmol) and Bu_4NCl (789 mg, 2.84 mmol). The mixture was refluxed for 3 h and extracted with a MeOH/EtOAc (5/95) solution. The organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (2/3) as eluent gave the tertiary alcohol **34** (750 mg, 77%) as a chocolaty waxy oil: R_f = 0.5 (EtOAc/hexane 1/1); IR (neat) ν_{max}/cm^{-1} 3379, 3253, 2950, 1734 (OC═O), 1458, 1318, 1162, 1024, 822, 744; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.0 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.0, 8.2 Hz, 1H), 6.91 (t, J = 7.0, 7.9 Hz, 1H), 6.59 (d, J = 16.2 Hz, 1H), 6.40 (d, J = 16.2 Hz, 1H), 4.77 (s, 1H), 3.74, (s, 2H), 3.32, (s, 3H), 1.26 (s, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.8 (OC═O), 138.8 (CH), 136.1 (C), 133.7 (C), 128.2 (C), 121.8 (CH), 118.7 (CH), 118.3 (CH), 114.0 (CH), 110.6 (CH), 105.9 (C), 69.3 (C), 51.6 (CH_3), 30.2 (2 CH_3), 29.4 (CH_2); HRMS m/z calcd for $C_{16}H_{19}NO_3$ [M + H − H_2O] 256.1400, found 256.1332.

*(E)-4-(3-(2-Hydroxyethyl)-1H-indol-2-yl)-2-methylbut-3-en-2-ol (**28**).* To a solution of the tertiary alcohol **34** (1 g, 3.66 mmol) in anhydrous ether (20 mL) was added $LiAlH_4$ (167 mg, 4.39 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, quenched with a solution of NH_4Cl, and extracted with EtOAc; the organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (7/3) as eluent gave the alcohol **28** (750 mg, 75%) as a white semisolid: R_f = 0.35 (EtOAc/hexane 3/2); IR (neat) ν_{max}/cm^{-1} 3329, 3053, 2973, 1613, 1457, 1378, 1150, 906, 741, 702; ^1H NMR (CD_3CN, 500 MHz) δ 9.11 (br s, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.1 (d, J = 8.2 Hz, 1H), 6.91 (dt, J = 7.0, 7.9 Hz, 1H), 6.8 (dt, J = 7.9, 7.9 Hz, 1H), 6.53 (d, J = 16.2 Hz, 1H), 6.06 (d, J = 16.5 Hz, 1H), 3.48 (q, J = 7.0, 6.1 Hz, 2H), 2.92, (s, 1H), 2.77 (t, J = 7.0 Hz, 2H), 2.66 (t, J = 5.8 Hz, 1H), 1.17 (s, 6H); ^{13}C NMR (CD_3CN, 125 MHz) δ 137.9 (CH), 137.6 (C), 134.2 (C), 129.9 (C), 123.2 (CH), 119.9 (CH), 119.6 (CH), 115.7 (CH), 112.3 (C), 111.5 (CH), 71.5 (C), 63.3 (CH_2), 30.4 (2 CH_3), 28.5 (CH_2); HRMS m/z calcd for $C_{15}H_{19}NO_2$ [M − H$^+$] 244.1316, found 244.1333.

*2-((6R,6aS,10aS)-6-(3-(2-Hydroxyethyl)-1H-indol-2-yl)-7,7,9-trimethyl-6a,7,8,10a-tetrahydro-6H-isoindolo[2,1-a]indol-11-yl)-ethanol (**35a**), 2-((6S,6aS,10aS)-6-(3-(2-Hydroxyethyl)-1H-indol-2-yl)-7,7,9-trimethyl-6a,7,8,10a-tetrahydro-6H-isoindolo[2,1-a]indol-11-yl)ethanol (**35b**), 2-((1R,3R)-3-((E)-2-(3-(2-Hydroxyethyl)-1H-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethanol (**36a**), and 2-((1R,3S)-3-((E)-2-(3-(2-Hydroxyethyl)-1H-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethanol (**36b**).* **35a**: to a solution of the alcohol **28** (500 mg, 2.04 mmol) in anhydrous CH_2Cl_2 (10 mL) was added a catalytic amount of $BF_3 \cdot OEt_2$ (28 mg, 0.20 mmol), and the mixture was stirred magnetically for 15 min at room temperature. The progress of the reaction was monitored by TLC until the starting alcohol had been completely consumed. A saturated solution of $NaHCO_3$ (10 mL) was then added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (3/7) as eluent furnished the isomer **35a** (165 mg, 36%) as a white semisolid: R_f = 0.5 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3377, 2922, 2851, 1457, 1298, 1149, 739; ^1H NMR

(CD_3CN, 500 MHz) δ 9.16 (br s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.10−7.03 (m, 2H), 6.86 (t, *J* = 7.9, 7.0 Hz, 1H), 6.69 (t, *J* = 7.9, 7.3 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.53 (s, 1H), 5.52 (s, 1H), 4.11 (br s, 1H), 3.87−3.73 (m, 4H), 3.12−3.05 (m, 3H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.81 (br s, 1H), 2.29−2.25 (br d, 1H), 1.78−1.72 (br d, 1H), 1.70 (s, 3H), 1.27 (s, 1H), 1.09 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 144.1 (C), 137.2 (C), 135.1 (C), 133.7 (C), 133.6 (C), 133.5 (C), 129.4 (C), 122.9 (CH), 120.9 (CH), 120.3 (CH), 120.1 (C and CH), 119.5 (CH), 119.4 (CH), 112.0 (CH), 111.9 (CH), 110.3 (CH), 102.9 (C), 63.3 (CH_2), 62.9 (CH_2), 59.2 (CH), 54.9 (CH), 41.2 (CH_2), 37.9 (CH_3), 32.7 (C), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_3), 27.7 (CH_3), 24.0 (CH); HRMS *m*/*z* calcd for $C_{30}H_{34}N_2O_2$ [M + H$^+$] 455.2720, found 455.2697.

36a: further elution of the column with EtOAc/hexane (4/6) gave the isomer **36a** (140 mg, 31%) as a white semisolid: R_f = 0.4 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3405, 2928, 1454, 1344, 1041, 741; ^{1}H NMR (CD_3CN, 500 MHz) δ 9.22 (br s, 1H), 7.51 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 5.5, 2.4 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.06 (t, *J* = 8.2 Hz, 1H), 7.00−6.98 (m, 2H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 6.00 (d, *J* = 16.2 Hz, 1H), 5.28 (d, *J* = 9.4 Hz, 1H), 4.22 (q, *J* = 8.8 Hz, 1H), 3.65 (br s, 2H), 3.44 (br s, 2H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.80−2.58 (m, 3H), 2.26 (dd, *J* = 8.5, 3.9 Hz, 1H), 2.19 (br s, 1H), 1.92 (s, 3H), 1.77 (d, 6H); ^{13}C NMR (CD_3CN, 125 MHz) δ 145.1 (C), 137.6 (C), 134.4 (C), 134.3 (C), 133.5 (C), 132.7 (C), 132.1 (CH), 129.6 (C), 126.0 (CH), 123.5 (CH), 121.1 (CH), 120.0 (CH), 119.7 (CH), 119.6 (CH), 119.5 (CH), 117.8 (CH), 113.2 (C), 111.6 (CH), 111.2 (CH), 104.1 (C), 64.8 (C), 63.6 (CH_2), 63.2 (CH_2), 51.9 (CH), 35.7 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 25.9 (2 CH_3), 18.3 (CH3); HRMS *m*/*z* calcd for $C_{30}H_{34}N_2O_2$ [M + H$^+$] 455.2720, found 455.2691.

36b: further elution of the column with EtOAc/hexane (2/3) gave the isomer **36b** (30 mg, 7%) as a white semisolid: R_f = 0.35 (EtOAc/hexane 2/3); IR (neat) ν_{max}/cm^{-1} 3319, 2925, 1454, 1317, 1041, 1011, 741; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (br s, 1H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.25 (dd, *J* = 8.0, 3.4 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.11−7.01 (m, 3H), 6.70 (d, *J* = 16.6 Hz, 1H), 6.29 (d, *J* = 16.3 Hz, 1H), 5.27 (d, *J* = 9.4 Hz, 1H), 4.28 (q, *J* = 9.1 Hz, 1H), 3.85−3.78 (m, 4H), 3.02−2.87 (m, 4H), 2.71 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.38 (dd, *J* = 8.0, 4.5 Hz, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.6 (C), 136.4 (C), 133.5 (C), 133.2 (C), 132.4 (CH), 132.3 (C), 131.3 (C), 128.6 (C), 125.0 (CH), 123.2 (CH), 120.5 (CH), 119.7 (CH), 118.9 (CH), 118.8 (CH), 118.7 (CH), 118.1 (CH), 112.2 (C), 110.6 (CH), 109.9 (CH), 102.4 (C), 63.2 (CH_2), 63.0 (CH_2), 62.9 (C), 51.7 (CH_2), 35.2 (CH_3), 27.6 (CH_2), 27.3 (CH_2), 25.7 (CH_3), 23.2 (CH_3), 18.1 (CH); HRMS *m*/*z* calcd for $C_{30}H_{34}N_2O_2$ [M + H$^+$] 455.2720, found 455.2693.

35b: again, further elution of the column with EtOAc/hexane (7/3) gave the isomer **35b** (35 mg, 8%) as a yellow semisolid: R_f = 0.3 (EtOAc/hexane 1/1); IR (neat) ν_{max}/cm^{-1} 3374, 2926, 1457, 1376, 1299, 1010, 739; ^{1}H NMR (CD_3CN, 500 MHz) δ 9.06 (br s, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.08−7.01 (m, 2H), 6.84 (td, *J* = 7.9, 7.0, Hz, 1H), 6.67 (td, *J* = 7.8, 7.0 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 5.99 (d, *J* = 9.4 Hz, 1H), 5.39 (dt, *J* = 11.3, 2.4 Hz, 1H), 4.45 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.91−3.80 (m, 2H), 3.64−3.57 (m, 2H), 3.31 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.14 (t, *J* = 6.7 Hz, 2H), 3.08 (br s, 1H), 2.96 (s, 1H), 2.81 (td, *J* = 7.3, 3.0 Hz, 2H), 2.62 (br s, 1H), 1.88 (s, 3H), 1.26 (s, 3H), 1.24 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 144.4 (C), 137.4 (C), 135.2 (C), 133.5 (C), 133.4 (C), 131.6 (C), 129.1 (C), 123.7 (CH), 122.9 (CH), 120.9 (CH), 120.0 (CH), 119.9 (CH), 119.4 (CH), 119.3 (CH), 112.5 (C), 112.0 (CH), 110.2 (CH), 102.9 (C), 72.0 (CH), 64.9 (CH), 63.1 (CH_2), 62.8 (CH_2), 54.0 (CH), 39.4 (CH_2), 30.1 (C), 29.0 (CH_2), 28.5 (CH_2), 28.1 (CH_3), 26.0 (CH_3), 18.1 (CH_3); HRMS *m*/*z* calcd for $C_{30}H_{34}N_2O_2$ [M + H$^+$] 455.2720, found 455.2692.

*2-(2-((6R,6aS,10aS)-7,7,9-Trimethyl-11-(2-oxoethyl)-6a,7,8,10a-tetrahydro-6H-isoindolo[2,1-a]indol-6-yl)-1H-indol-3-yl)-acetaldehyde (**41**).* To a solution of the alcohol **35a** (90 mg, 0.198 mmol) in ethyl acetate (10 mL) was added IBX (222 mg, 0.792 mmol), and the mixture was refluxed for 1 h. Aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/4) as eluent furnished the dial **41** (72 mg, 80%) as a yellow waxy oil: R_f = 0.6 (EtOAc/hexane 1/3); IR (neat) ν_{max}/cm^{-1} 3389, 2961, 2925, 1718 (C═O), 1456, 1333, 1240, 1167, 1048, 740; ^{1}H NMR (CD_3CN, 500 MHz) δ 9.75−9.73 (m, 2H), 9.39 (br s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.15 (td, *J* = 8.2, 7.0 Hz, 1H), 7.08 (t, *J* = 7.9, Hz, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 6.77 (td, *J* = 9.2, 7.9 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 5.54 (d, *J* = 8.5 Hz, 1H), 5.45−5.44 (m, 1H), 4.12−4.10 (m, 1H), 3.97 (s, 2H), 3.86 (t, *J* = 2.4 Hz, 2H), 3.14 (t, *J* = 7.9 Hz, 1H), 2.26 (br d, 1H), 1.78 (br d, 1H), 1.70 (s, 3H), 1.09 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 200.4 (HC═O), 200.3 (HC═O), 145.4 (C), 137.2 (C), 136.1 (C), 134.2 (C), 133.5 (C), 133.4 (C), 129.2 (C), 123.5 (CH), 121.6 (CH), 120.6 (CH), 120.2 (CH), 119.9 (CH), 119.7 (CH), 119.2 (CH), 112.3 (CH), 110.5 (CH), 106.3 (C), 96.6 (C), 59.2, 55.0, 41.1, 40.2, 40.2, 37.9, 32.6, 28.8, 27.8, 24.0; HRMS *m*/*z* calcd for $C_{30}H_{30}N_2O_2$ [M + H$^+$] 451.2400, found 451.2388.

*Dimethylisoborreverine (**6**).* To a mixture of $NHMe_2$ (0.26 mL, 2.0 M solution, 0.53 mmol) and $NaCNBH_3$ (32 mg, 0.53 mmol) in MeOH (2 mL) and acetic acid (0.01 mL) was added a solution of the dialdehyde **41** (60 mg, 0.13 mmol) in MeOH (2 mL), and this mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (2 × 5 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using $MeOH/CH_2Cl_2$ (1/9) as eluent furnished the compound dimethylisoborreverine (**6**; 55 mg, 82%) as a white semisolid: R_f = 0.3 ($MeOH/CH_2Cl_2$ 1/9); IR (neat) ν_{max}/cm^{-1} 3427, 2255, 1651, 1049, 1025, 1003, 826, 764, 631; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.01 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 5.43 (br s, 1H), 5.35 (d, *J* = 9.2 Hz, 1H), 4.02 (br s, 1H), 3.15 (t, *J* = 8.8 Hz, 1H), 2.87−2.83 (m, 4H), 2.59−2.45 (m, 5H), 2.24 (s, 6H), 2.13 (s, 6H), 1.69 (br d, 1H), 1.65 (s, 3H), 1.02 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 141.8 (C), 135.9 (C), 132.9 (C), 131.9 (2 CH), 127.7 (C), 121.3, 119.7, 119.3, 118.6, 118.4 (2 CH), 118.2, 118.1, 111.2 (C), 111.1 (CH), 109.1 (CH), 102.8 (C), 60.3, 59.6, 57.0, 53.6, 45.2 (2 N−CH_3), 45.1 (2 N−CH_3), 39.3 (CH_2, merged in DMSO-d_6), 36.4, 31.4, 28.4, 27.3, 23.7, 22.5, 22.3; HRMS *m*/*z* calcd for $C_{34}H_{44}N_4$ [M + H$^+$] 509.3666, found 509.3644.

*Dimethylisoborreverine (**6**):* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.46 (br s, 1H), 7.66 (dd, *J* = 8.8, 4.5 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.21−7.14 (m, 3H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 5.47 (br s, 1H), 5.45 (d, *J* = 8.9 Hz, 1H), 4.05 (br s, 1H), 3.13−3.00 (m, 5H), 2.82−2.66 (m, 4H), 2.40 (s, 6H), 2.37 (s, 6H), 2.19 (br d, 1H), 1.79 (br d, 1H), 1.71 (s, 3H), 1.11 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.2 (C), 136.3 (C), 133.3 (C), 132.7 (C), 132.6 (C), 132.2 (C), 128.1 (C), 122.2 (CH), 120.7 (CH), 119.3 (CH), 119.0 (2 CH), 118.9 (CH), 118.3 (CH), 112.2 (C), 111.4 (CH), 109.8 (CH), 103.1 (C), 60.4 (CH_2), 60.0 (CH_2), 59.0 (CH), 53.8 (CH), 45.5 (2 N−CH_3), 45.5 (2 N−CH_3), 41.0 (CH_2), 37.2 (CH), 32.0 (C), 28.9 (CH_3), 27.4 (CH_3), 24.0 (CH_3), 23.5 (CH_2), 23.0 (CH_2).

*Dimethylisoborreverine (**6**), TFA Salt.* Dimethylisoborreverine (**6**; 10 mg) was treated with a 0.5 M solution of TFA in acetonitrile to obtain the TFA salt of dimethylisoborreverine: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.21 (br s, 1H), 10.20 (br s, 1H, TFA proton), 10.10 (br s, 1H, TFA proton), 7.67 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.02 (dd, *J* = 7.6, 7.0 Hz, 1H), 6.88 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.71 (dd, *J* = 7.6, 7.3 Hz, 1H), 6.22 (d, *J* = 7.9 Hz, 1H), 5.49 (d, *J* = 9.5 Hz, 1H), 5.46 (m, 1H), 4.11 (br s, 1H), 3.40−3.26 (m, 2H), 3.25−2.90 (m, 8H), 2.92 (s, 6H), 2.82 (s, 6H), 2.28 (d, *J* = 14.0 Hz, 1H), 1.69 (br s, 3H), 1.04 (s, 3H), 0.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.9, 135.8, 133.9, 132.1, 131.8, 131.3, 126.9, 121.7, 120.2, 118.9, 118.7, 118.5, 118.5, 118.1, 111.3, 108.9, 107.2, 99.0, 57.1, 56.6, 56.1, 53.5, 42.1 (2 N−CH_3), 41.9 (N−CH_3), 41.8 (N−CH_3), 39.0 (CH_2), 38.9 (CH), 36.2 (C), 31.4 (CH_3), 28.2 (CH_3), 27.4 (CH_3), 23.5 (CH_2), 19.3 (CH_2).

Isoborreverine (5). To a stirred solution of dialdehyde **41** (60 mg, 0.13 mmol) and methylamine (0.33 mL, 2.0 M solution, 0.66 mmol) in CH_2Cl_2 (6 mL) was added $NaBH_4$ (25 mg, 0.66 mmol) followed by $Fe(OTf)_3$ (20 mg, 0.04 mmol) sequentially, and the mixture was stirred for 5−10 min at room temperature. Thereafter, MeOH (1 mL) was added to drive the reaction to completion. After completion of the reaction (TLC), the reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 10 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1.5/8.5) as eluent furnished the compound isoborreverine (**5**; 57 mg, 89%) as a yellow solid: R_f = 0.3 (MeOH/CH_2Cl_2 1/4); mp 107−109 °C; IR (neat) ν_{max}/cm^{-1} 3428, 1651, 1026, 1004, 826, 764; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.05 (br s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6, Hz, 1H), 6.97 (t, J = 7.6, Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.64 (t, J = 7.9 Hz, 1H), 6.28 (d, J = 8.2 Hz, 1H), 5.44 (s, 1H), 5.39 (d, J = 9.2 Hz, 1H), 4.04 (s, 1H), 3.14 (br t, 1H), 2.93−2.74 (m, 8H), 2.46 (s, 6H), 2.42 (s, 2H), 1.66 (s, 3H), 1.01 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 143.0 (C), 136.7 (C), 134.0 (C), 132.8 (CH), 132.7 (C), 128.5, 122.1, 120.5, 120.0, 119.5, 119.2, 119.0 (2 CH), 118.9, 111.9 (C and CH), 109.8 (CH), 103.0 (C), 57.8 (CH), 52.7 (CH), 52.6 (2 CH_2), 37.2 (CH_2), 36.3 (CH), 36.3 (2 CH_3), 32.2 (C), 29.2 (CH_3), 28.1 (CH_3), 25.0 (CH_2), 24.8 (CH_2), 24.4 (CH_3); HRMS m/z calcd for $C_{32}H_{40}N_4$ [M + H$^+$] 481.3400, found 481.3335.

Isoborreverine (5), TFA Salt. Isoborreverine (**5**; 10 mg) was treated with a 0.5 M solution of TFA in acetonitrile to obtain the TFA salt of isoborreverine: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.13 (br s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 7.6, Hz, 1H), 7.00 (t, J = 7.6, Hz, 1H), 6.85 (t, J = 7.9 Hz, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.18 (d, J = 8.2 Hz, 1H), 5.44 (s, 1H), 5.41 (d, J = 9.2 Hz, 1H), 4.06 (s, 1H), 3.16−3.03 (m, 8H), 2.66 (br t, 3H), 2.58 (s, 3H), 2.45 (s, 2H), 2.24 (br d, 1H), 1.67 (s, 3H), 1.01 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 143.4, 134.3, 132.8, 132.5, 132.1, 122.3, 120.8, 119.5, 119.3, 119.2, 119.1, 118.6, 118.2, 115.9, 111.9, 109.5, 100.1 (2 C), 57.6 (CH), 49.3 (2 CH_2), 48.8 (CH), 36.9 (CH_2), 32.9 (CH and CH_3), 32.8 (2 CH_3), 32.0, 28.8, 27.9, 24.1, 21.5.

Isoborreverine (5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (br s, 1H), 7.69 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.14 (m, 3H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (t, J = 7.9, Hz, 1H), 6.45 (d, J = 8.2, Hz, 1H), 5.47 (br s, 1H), 5.45 (s, 1H), 4.06 (br s, 1H), 3.30−2.80 (m, 10H), 2.47 (s, 3H), 2.39 (s, 3H), 2.19 (br d, 1H), 1.70 (s, 3H), 1.10 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4 (C), 136.8 (C), 134.0 (C), 133.3 (C), 133.2 (C), 132.8 (C), 128.9 (C), 122.8 (CH), 121.3 (CH), 119.9 (CH), 119.6 (CH), 119.6 (CH), 119.6 (CH), 119.0 (CH), 112.7, 111.8, 110.2 (CH), 103.1 (C), 59.6 (CH), 54.5 (CH), 53.1 (CH_2), 52.6 (CH_2), 41.5 (CH_2), 37.7 (CH), 37.0 (N−CH_3), 36.6 (N−CH_3), 32.5 (C), 29.5 (CH_3), 28.0 (CH_3), 26.0 (CH_2), 25.1 (CH_2), 24.5 (CH_3).

2-((1R,3R)-3-Methyl-1-(2-methylprop-1-enyl)-3-((E)-2-(3-(2-oxoethyl)-1H-indol-2-yl)vinyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)acetaldehyde (42a). To a solution of the alcohol **36a** (30 mg, 0.066 mmol) in ethyl acetate (5 mL) was added IBX (74 mg, 0.264 mmol), and the mixture was refluxed for 1 h. Aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/4) as eluent furnished the compound **42a** (22 mg, 74%) as a yellow semisolid: R_f = 0.6 (EtOAc/hexane 1/3); IR (neat) ν_{max}/cm^{-1} 3390, 2923, 1720 (C═O), 1454, 1344, 741; ^{1}H NMR (CD_3CN, 500 MHz) δ 9.60 (t, J = 2.3 Hz, 1H), 9.45 (t, J = 2.0 Hz, 1H), 9.4 (br s, 1H), 7.42−7.35 (ddd, J = 13.2, 9.4, 7.7 Hz, 3H), 7.27 (d, J = 8.3 Hz, 1H), 7.11 (td, J = 8.0, 7.2 Hz, 1H), 7.05−6.96 (m, 3H), 6.36 (d, J = 16.0 Hz, 1H), 6.07 (d, J = 16.3 Hz, 1H), 5.23 (dt, J = 9.7, 2.8 Hz, 1H), 4.23 (q, J = 8.6 Hz, 1H), 3.66−3.60 (m, 4H), 2.84 (dd, J = 8.0, 4.6 Hz, 1H), 2.31 (dd, J = 8.6, 4.0 Hz, 1H), 1.94 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 200.7 (HC═O), 199.8 (HC═O), 146.3 (C), 137.6 (C), 135.1 (C), 134.4 (C), 134.2 (C), 133.5 (CH), 132.7 (C), 129.6 (C), 125.4 (CH), 123.9 (CH), 121.6 (CH), 120.6 (CH), 120.1 (CH), 119.5 (CH), 119.4 (CH), 117.4 (CH), 111.8 (CH), 111.4 (CH), 106.5 (C), 97.7 (C), 65.2 (C), 51.7 (CH), 39.7 (CH_2), 39.5 (CH_2), 35.8 (CH_2), 25.8 (CH_3), 25.8 (CH_3), 18.4 (CH_3); HRMS m/z calcd for $C_{30}H_{30}N_2O_2$ [M + H$^+$] 451.2400, found 451.2386.

Flinderole A (1). To a stirred solution of dialdehyde **42a** (30 mg, 0.066 mmol) and methylamine (0.16 mL, 2.0 M solution, 0.33 mmol) in CH_2Cl_2 (3 mL) was added $NaBH_4$ (12 mg, 0.33 mmol) followed by $Fe(OTf)_3$ (10 mg, 0.02 mmol) sequentially, and the mixture was stirred for 5−10 min at room temperature. Thereafter, MeOH (1 mL) was added to drive the reaction to completion. After completion of the reaction (TLC), the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 5 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1.5/8.5) as eluent furnished the compound flinderole A (**1**; 24 mg, 75%) as a white semisolid: R_f = 0.3 (MeOH−CH_2Cl_2 1:4); IR (neat) ν_{max}/cm^{-1} 3419, 2256, 2129, 1651, 1048, 1025, 1001, 826, 765, 631; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.94 (s, 1H), 7.46 (dd, J = 7.0, 1.8 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.34 (dd, J = 6.4, 1.5 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.00 (t, J = 7.9 Hz, 1H), 6.97−6.91 (m, 2H), 6.87 (t, J = 7.0 Hz, 1H), 6.40 (d, J = 16.2 Hz, 1H), 6.07 (d, J = 16.2 Hz, 1H), 5.25 (d, J = 9.7 Hz, 1H), 4.15 (q, J = 8.9, Hz, 1H), 3.35 (br t, J = 5.2 Hz, 1H), 2.78−2.60 (m, 8H), 2.29 (s, 3H), 2.25 (dd, J = 8.8, 3.9 Hz, 1H), 2.15 (s, 3H), 1.90 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 142.9 (C), 136.4 (C), 132.7 (C), 132.4 (C), 131.9 (C), 131.1 (CH), 131.0 (C), 128.1 (C), 125.1 (CH), 122.0 (CH), 119.9 (CH), 118.5 (CH), 118.4 (CH), 118.4 (CH), 118.3 (CH), 116.5 (CH), 112.5 (C), 110.1 (CH), 110.0 (CH), 103.6 (C), 63.4 (C), 60.7 (CH_2), 52.4 (CH_2), 50.8 (CH_2), 35.6 (N−CH_3), 35.5 (N−CH_3), 34.4 (CH), 29.2 (CH_2), 25.5 (CH_3), 25.1 (CH_3), 23.4 (CH_2), 18.0 (CH_3); HRMS m/z calcd for $C_{32}H_{40}N_4$ [M + H$^+$] 481.3353, found 481.3333.

Flinderole A (1), TFA Salt. Flinderole A (**1**; 10 mg) was treated with a 0.5 M solution of TFA in acetonitrile to obtain the TFA salt of flinderole A: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.24 (br s, 1H), 8.78 (m, 2H), 7.58 (d, J = 7.7 Hz, 1H), 7.54 (br d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.25 (br d, J = 7.7 Hz, 1H), 7.08 (dd, J = 7.7, 7.7 Hz, 1H), 7.04 (dd, J = 6.3, 6.3 Hz, 1H), 7.02 (dd, J = 6.3, 6.3 Hz, 1H), 6.98 (dd, J = 7.4, 7.4 Hz, 1H), 6.58 (d, J = 16.3 Hz, 1H), 6.52 (d, J = 16.3 Hz, 1H), 5.32 (d sept, J = 8.9, 1.2 Hz, 2H), 4.30 (ddd, J = 8.9, 8.3, 8.0 Hz, 1H), 2.99 (m, 2H), 2.90 (dd, J = 12.9, 8.0 Hz, 2H), 2.90 (br t, J = 8.0 Hz, 1H), 2.62 (br t, 3H), 2.57 (m, 1H), 2.56 (br t, 3H), 2.31 (dd, J = 12.6, 7.7 Hz, 1H), 1.96 (s, 3H), 1.85 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 143.6, 136.4, 133.1, 132.4, 132.2, 132.1, 130.9, 127.6, 124.9, 122.4, 120.3, 118.8, 118.6, 118.3, 118.2, 116.4, 110.8, 110.1, 109.2, 100.3, 63.3 (C), 50.6 (CH_2), 48.8 (CH_2), 34.5, 32.4 (CH), 32.3 (2 N−CH_3), 25.4 (CH_2), 24.6 (CH_3), 20.3 (CH_3), 20.2 (CH_2), 18.0 (CH_3).

Flinderole B (2). To a mixture of $NHMe_2$ (0.26 mL, 2.0 M solution, 0.53 mmol) and $NaCNBH_3$ (32 mg, 0.53 mmol) in MeOH (2 mL) and acetic acid (0.01 mL) was added a solution of the dialdehyde **42a** (60 mg, 0.13 mmol) in MeOH (2 mL), and this mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (2 × 5 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1/9) as eluent furnished the compound flinderole B (**2**; 58 mg, 85%) as a white waxy solid: R_f = 0.4 (MeOH/CH_2Cl_2 1/4).

2-((1R,3S)-3-Methyl-1-(2-methylprop-1-enyl)-3-((E)-2-(3-(2-oxoethyl)-1H-indol-2-yl)vinyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)acetaldehyde (42b). To a solution of the alcohol **36b** (100 mg, 0.22 mmol) in ethyl acetate (10 mL) was added IBX (246 mg, 0.88

mmol), and the mixture was refluxed for 1 h. Aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (3/7) as eluent furnished the dial **42b** (80 mg, 81%) as a white semisolid: R_f = 0.6 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3385, 2926, 2722, 1721 (C═O), 1454, 1343, 1079, 742; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (t, J = 2.7 Hz, 1H), 9.65 (t, J = 2.4 Hz, 1H), 8.25 (br s, 1H), 7.49 (dd, J = 7.6, 7.0 Hz, 2H), 7.30−7.21 (m, 3H), 7.15−7.05 (m, 3H), 6.71 (d, J = 16.5 Hz, 1H), 6.36 (d, J = 16.2 Hz, 1H), 5.21 (d, J = 9.4 Hz, 1H), 4.30 (q, J = 8.5 Hz, 1H), 3.83 (d, J = 2.4 Hz, 2H), 3.66 (s, 2H), 2.72 (dd, J = 7.9, 4.8 Hz, 1H), 2.40 (dd, J = 8.8, 3.9 Hz, 1H), 1.82 (s, 3H), 1.78 (s, 3H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9 (CHO), 198.6 (CHO), 144.3 (C), 136.3 (C), 134.4 (C), 133.6 (CH), 133.0 (C), 132.8 (C), 131.3 (C), 128.7 (C), 124.1 (CH), 123.8 (CH), 120.9 (CH), 120.4 (CH), 119.5 (CH), 118.6 (CH), 118.4 (CH), 117.8 (CH), 110.8 (CH), 110.0 (CH), 105.9 (C), 96.5 (C), 63.3 (C), 51.7 (CH_2), 39.4 (CH_2), 38.9 (CH_2), 35.3 (CH_3), 25.7 (CH_3), 22.9 (CH_3), 18.3 (CH); HRMS m/z calcd for $C_{30}H_{30}N_2O_2$ [M + H$^+$] 451.2407, found 451.2389.

Desmethyl Flinderole C. To a stirred solution of dialdehyde **42b** (30 mg, 0.066 mmol) and methylamine (0.16 mL, 2.0 M solution, 0.33 mmol) in CH_2Cl_2 (3 mL) was added $NaBH_4$ (12 mg, 0.33 mmol) followed by $Fe(OTf)_3$ (10 mg, 0.02 mmol) sequentially, and the mixture was stirred for 5−10 min at room temperature. Thereafter, methanol (1 mL) was added to drive the reaction to completion. After completion of the reaction (TLC), the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 5 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using $MeOH/CH_2Cl_2$ (1.5/8.5) as eluent furnished the compound desmethyl flinderole C (22 mg, 69%) as a white semisolid: R_f = 0.3 ($MeOH/CH_2Cl_2$ 1/4); IR (neat) ν_{max}/cm^{-1} 2921, 2851, 1575, 1456, 1377, 1259, 1097, 802, 742; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.03 (s, 1H), 7.49 (br d, J = 7.9 Hz, 1H), 7.47−7.45 (m, 1H), 7.26−7.24 (m, 1H), 7.23 (br d, J = 8.2 Hz, 1H), 7.06 (td, J = 8.2, 7.0 Hz, 1H), 6.96−6.92 (m, 3H), 6.73 (d, J = 16.2 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 5.26 (d, J = 9.4 Hz, 1H), 4.33 (q, J = 9.4 Hz, 1H), 2.86 (br t, J = 8.5, 5.5 Hz, 2H), 2.75−2.60 (m, 8H), 2.32 (s, 3H), 2.28 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 142.6 (C), 136.5 (C), 132.8 (C), 132.4 (CH), 132.2 (C), 132.0 (C), 130.8 (C), 128.2 (C), 125.4 (CH), 122.2 (CH), 119.8 (CH), 118.6 (CH), 118.5 (CH), 118.4 (CH), 118.2 (CH), 117.9 (CH), 113.0 (C), 110.7 (CH), 109.8 (CH), 103.7 (C), 62.7 (C), 52.7 (CH_2), 52.6 (CH_2), 51.0 (CH_2), 35.8 (2 N−CH_3), 34.7 (CH), 25.5 (CH_3), 23.8 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 18.0 (CH_3); HRMS m/z calcd for $C_{32}H_{40}N_4$ [M + H$^+$] 481.3353, found 481.3337.

Flinderole C (3). To a mixture of $NHMe_2$ (0.26 mL, 2.0 M solution, 0.53 mmol) and $NaCNBH_3$ (32 mg, 0.53 mmol) in MeOH (2 mL) and acetic acid (0.01 mL) was added a solution of the dialdehyde **42b** (60 mg, 0.13 mmol) in MeOH (2 mL), and this mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (2 × 5 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using $MeOH/CH_2Cl_2$ (1/9) as eluent furnished flinderole C (**3**; 55 mg, 81%) as a colorless waxy solid: R_f = 0.4 ($MeOH/CH_2Cl_2$ 1/4).

Ethyl 2-(1-(Phenylsulfonyl)-1H-indol-3-yl)ethylcarbamate (45). To a magnetically stirred solution of the tryptamine acetate **44a** (12 g, 51.7 mmol) in THF (120 mL) was added KOH powder (14.5 g, 258.6 mmol) followed by dropwise addition of $PhSO_2Cl$ (19.8 mL, 155.2 mmol) at 0 °C, and the mixture was stirred magnetically for 6 h at room temperature. Water (100 mL) was then added to the reaction mixture, which was then extracted with EtOAc (3 × 100 mL), washed with brine (100 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1/4) as eluent furnished compound **45** (17.5 g, 91%) as a yellow solid: R_f = 0.4 (EtOAc/hexane 3/7); mp 94−96 °C; IR (neat) ν_{max}/cm^{-1} 3336, 2923, 1698 (NHC═O), 1525, 1447, 1174, 746, 601, 571; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.47 (t, J = 7.9 Hz, 2H), 7.38−7.36 (m, 3H), 7.30 (t, J = 7.9 Hz, 1H), 7.21 (br t, J = 7.0 Hz, 1H), 4.96 (br s, 1H), 4.09 (br d, J = 6.1 Hz, 2H), 3.43 (br d, J = 5.2 Hz, 2H), 2.85 (br s, 2H), 1.20 (br s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5 (OC═O), 137.8 (C), 135.1 (C), 133.6 (CH), 130.6 (C), 129.1 (2 CH), 126.5 (2 CH), 124.7 (CH), 123.2 (CH), 123.1 (CH), 119.9 (C), 119.3 (CH), 113.5 (CH), 60.6 (CH_2), 40.0 (CH_2), 25.4 (CH_2), 14.5 (CH_3); HRMS m/z calcd for $C_{19}H_{20}N_2O_4S$ [M + H$^+$] 373.1200, found 373.1221.

Ethyl 2-(2-Formyl-1-(phenylsulfonyl)-1H-indol-3-yl)-ethylcarbamate (46). To a magnetically stirred solution of the protected tryptamine **45** (10 g, 26.9 mmol) in CH_2Cl_2 (100 mL) was added dichloromethyl methyl ether (12 mL, 134.4 mmol) followed by dropwise addition of $SnCl_4$ (15.7 mL, 134.4 mmol) at −78 °C; the mixture was then warmed slowly to −10 °C over a period of 1 h. HCl (1.0 N, 100 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2. The organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and recrystallization of the crude product from 1,2-dichloroethane furnished the aldehyde **46** (8 g, 74%) as a white semisolid: R_f = 0.3 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 3425, 2982, 1705 (HC═O), 1418, 1349, 1171, 1016, 721, 593; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 1H), 7.60 (m, 3H), 7.43 (t, J = 7.7, 8.0 Hz, 1H), 7.29 (t, J = 8.3, 7.1 Hz, 3H), 7.13−7.08 (m, 2H), 6.30 (br s, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.87 (t, J = 8.0 Hz, 1H), 2.83 (br s, 1H), 2.20 (q, J = 8.3 Hz, 1H), 1.98 (dd, J = 7.1, 5.1 Hz, 1H), 1.25 (br s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.3 (CHO), 153.7 (NHC═O), 142.2 (2 C), 137.1 (2 C), 133.2 (CH), 129.8 (2 CH), 128.8 (2 CH), 126.8 (2 CH), 125.7 (C), 124.4 (CH), 79.3 (CH), 61.8 (CH_2), 44.8 (CH_2), 33.3 (CH_2), 14.2 (CH_3); HRMS m/z calcd for $C_{20}H_{20}N_2O_5S$ [M + H$^+$] 401.1200, found 401.1170.

(E)-Ethyl 3-(3-(2-(Ethoxycarbonylamino)ethyl)-1-(phenylsulfonyl)-1H-indol-2-yl)acrylate (47). To a solution of the aldehyde **46** (10 g, 25 mmol) in anhydrous CH_2Cl_2 (100 mL) was added dry Ph_3P═$CHCO_2Et$ (17 g, 50 mmol), and the mixture was stirred magnetically for 6 h at room temperature. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (3/7) as eluent gave the ester **47** (9.5 g, 81%) as a white crystalline solid: R_f = 0.45 (EtOAc -hexane 2:3); mp 75−77 °C; IR (neat) ν_{max}/cm^{-1} 2980, 1712 (OC═O), 1653 (NHC═O), 1416, 1367, 1110, 756, 689, 594; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, J = 8.0 Hz, 1H), 7.54 (br s, 2H), 7.32−7.25 (m, 2H), 7.22 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.52 (d, J = 15.7 Hz, 1H), 5.88 (br s, 1H), 4.88 (d, J = 15.7 Hz, 1H), 4.14 (q, J = 7.1, 6.8 Hz, 2H), 4.03 (br q, 2H), 3.80 (dd, J = 7.4, 3.4 Hz, 1H), 2.79 (td, J = 5.7, 5.4 Hz, 1H), 2.09−2.00 (m, 2H), 1.26 (br t, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2 (OC═O), 154.0 (NHC═O), 146.6 (CH), 142.0 (2 C), 137.9 (2 C), 133.1 (CH), 132.4 (C), 129.4 (CH), 128.7 (2 CH), 127.1 (CH), 125.7 (CH), 124.6 (CH), 121.9 (CH), 118.5 (CH), 83.2 (CH), 61.8 (CH_2), 60.3 (CH_2), 45.5 (2 CH_2), 14.3 (CH_3), 14.0 (CH_3); HRMS m/z calcd for $C_{24}H_{26}N_2O_6S$ [M + H$^+$] 471.1600, found 471.1592.

(E)-Ethyl 2-(2-(3-Hydroxy-3-methylbut-1-enyl)-1-(phenylsulfonyl)-1H-indol-3-yl)ethylcarbamate (48). To a cold (0 °C), magnetically stirred solution of the ester **47** (11 g, 23.4 mmol) in anhydrous ether (100 mL) was added methylmagnesium iodide (prepared from magnesium turnings (2.8 g, 117.0 mmol), methyl iodide (8.7 mL, 140.4 mmol), and a few crystals of iodine in anhydrous ether (100 mL)), and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with aqueous NH_4Cl solution (100 mL) and worked up. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (9/1) as eluent furnished the tertiary alcohol **48** (8 g, 75%) as a thick yellowish semisolid: R_f = 0.3 (EtOAc only); IR (neat) ν_{max}/cm^{-1} 3416, 2974, 1702 (NHC═O), 1417, 1349, 1197, 690, 591, 542; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (br s, 1H), 7.65−7.61 (m, 1H), 7.52−7.47 (m, 2H), 7.43 (dd, J = 2.8, 2.8 Hz, 1H), 7.41−7.38 (m, 2H), 7.21 (td, J = 7.5, 1.5 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 6.6 Hz, 1H), 5.96 (br s, 1H), 5.38 (s, 2H), 4.18−4.06 (m, 2H), 3.84 (dd, J = 7.1, 2.8 Hz,

1H), 2.85 (td, J = 5.4, 5.1 Hz, 1H), 2.15−2.05 (m, 2H), 1.24 (t, J = 6.5 Hz, 3H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2 (NHC═O), 141.6 (C), 138.9 (CH), 134.4 (C), 132.8 (CH), 131.9 (CH), 131.8, 128.8, 128.6 (2 CH), 128.4, 128.3, 127.4, 127.0, 124.3, 116.6, 83.9 (CH), 70.1 (C), 61.6 (CH_2), 45.5 (2 CH_2), 29.5 (CH_3), 29.5 (CH_3), 14.3 (CH_3); HRMS m/z calcd for $C_{24}H_{28}N_2O_5S$ [M + H$^+$] 457.1800, found 457.1799.

*(E)-Ethyl 2-(2-(3-Methylbuta-1,3-dienyl)-1-(phenylsulfonyl)-1H-indol-3-yl)ethylcarbamate (**49**).* To a solution of the tertiary alcohol **48** (2 g, 4.38 mmol) in anhydrous THF (20 mL) and Et_3N (3.65 mL, 26.3 mmol) under an N_2 atmosphere was added MsCl (1.0 mL, 13.15 mmol) slowly over a period of 5 min at 0 °C. The solution was warmed to room temperature for about 1.5 h and then refluxed for 30 min. The precipitate that formed was filtered off using ethyl acetate, affording a brown viscous liquid. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/4) as eluent furnished the diene **49** (1.6 g, 83%) as a white semisolid: R_f = 0.5 (EtOAc/hexane 3/7); IR (neat) ν_{max}/cm^{-1} 2977, 1704 (NHC═O), 1476, 1349, 1196, 754, 688, 594; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (br d, 3H), 7.37 (td, J = 7.7 Hz, 1H), 7.30−7.25 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 5.92 (br s, 1H), 5.48 (d, J = 15.7 Hz, 1H), 5.32 (d, J = 16.0 Hz, 1H), 4.87 (s, 1H), 4.65 (s, 1H), 4.21−4.17 (m, 2H), 3.85 (dd, J = 6.3, 3.7 Hz, 1H), 2.88−2.81 (m, 1H), 2.15−2.07 (m, 2H), 1.61 (s, 3H), 1.33 (br t, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1 (NHC═O), 141.7 (C), 140.4 (2 C), 138.1 (C), 134.1 (C), 133.3 (CH), 133.2 (CH), 130.2 (CH), 128.7 (CH), 128.6 (C), 128.4 (3 CH), 127.0 (CH), 125.2 (CH), 124.6 (CH), 117.6 (CH_2), 84.0 (CH), 61.6 (CH_2), 45.5 (2 CH_2), 18.2 (CH_3), 14.3 (CH_3); HRMS m/z calcd for $C_{24}H_{26}N_2O_4S$ [M + H$^+$] 439.1700, found 439.1698.

*(E)-Ethyl 2-(2-(3-Methylbuta-1,3-dienyl)-1H-indol-3-yl)-ethylcarbamate (**50**).* To a solution of the diene **49** (3 g, 6.84 mmol) in anhydrous methanol (30 mL) were added Na_2HPO_4 (3.9 g, 27.39 mmol) and Na−Hg (7.7 g, 34.24 mmol). The reaction mixture was stirred for 1 h at room temperature. Water (20 mL) and ether (30 mL) were added, and the supernatant was decanted. The residue was washed with ether (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (3/7) as eluent gave the diene **50** (1.8 g, 90%) as a white semisolid: R_f = 0.4 (EtOAc/hexane 2/3); IR (neat) ν_{max}/cm^{-1} 3360, 2974, 1692 (NHC═O), 1609, 1421, 1201, 1112, 892, 7457; ^{1}H NMR (CD_3CN, 500 MHz; rotamers) δ 7.08−7.02 (m, 2H), 6.73 (td, J = 7.3, 6.7 Hz, 1H), 6.62 (t, J = 8.8 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 5.91 (d, J = 15.9 Hz, 1H), 5.37 (br d, 1H), 5.17 (s, 1H), 4.87 (br d, 2H), 4.16−4.03 (m, 2H), 3.70−3.62 (m, 1H), 2.96−2.89 (m, 1H), 2.29−2.24 (m, 2H), 1.78 (s, 3H), 1.25 (dt, J = 14.3, 7.0 Hz, 3H); ^{13}C NMR (CD_3CN, 125 MHz; rotamers) δ 155.7 (NHC═O), 155.0, 150.8, 150.7, 142.6, 133.4, 133.3, 132.6, 132.6, 131.5, 131.4, 129.5, 125.0, 119.7, 119.7, 117.1, 110.5, 110.4, 82.4, 81.9, 62.0, 61.8, 60.5, 59.4, 46.9, 46.7, 36.4, 36.1 (CH_2), 18.9 (CH_3), 15.1 (CH_3); HRMS m/z calcd for $C_{18}H_{22}N_2O_2$ [M + H$^+$] 299.1800, found 299.1760.

*(E)-N-Methyl-2-(2-(3-methylbuta-1,3-dienyl)-1H-indol-3-yl)-ethanamine (**43**).* To a solution of the *N*-acetate diene **50** (600 mg, 2.01 mmol) in anhydrous THF (10 mL) was added $LiAlH_4$ (10 mL, 1.0 M solution, 10.06 mmol), and the mixture was stirred magnetically for 3 h at room temperature. The progress of the reaction was monitored by TLC until the starting **53** had been completely consumed. Water (10 mL) was then added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1/9) as eluent furnished the diene **43** (320 mg, 66%) as a white semisolid: R_f = 0.3 (MeOH/CH_2Cl_2 1/9); IR (neat) ν_{max}/cm^{-1} 2927, 1607, 1486, 1466, 1244, 968, 743; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (dd, J = 8.0, 6.0 Hz, 2H), 6.77 (td, J = 7.4 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 6.12 (d, J = 15.7 Hz, 1H), 5.95 (d, J = 15.7 Hz, 1H), 4.91 (br d, 2H), 4.57 (s, 1H), 2.80−2.77 (m, 1H), 2.68 (dt, J = 6.0, 2.6 Hz, 1H), 2.47 (s, 3H), 2.38−2.31 (m, 1H), 2.12−2.07 (m, 1H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.1 (2 C), 141.6 (2 C), 134.9 (CH), 133.7 (C), 131.3 (CH), 127.9 (CH), 124.7 (CH), 119.0 (CH), 116.0 (CH_2), 109.4 (CH), 52.4 (CH_2), 39.8 (CH_2), 36.9 (CH_3), 18.7 (CH_3); HRMS m/z calcd for $C_{16}H_{20}N_2$ [M + H$^+$] 241.1700, found 241.1707.

*(E)-Ethyl 2-(2-(3-Hydroxy-3-methylbut-1-enyl)-1H-indol-3-yl)-ethylcarbamate (**51a**).* To a solution of the tertiary alcohol **48** (2 g, 4.38 mmol) in anhydrous methanol (30 mL) were added Na_2HPO_4 (2.5 g, 17.5 mmol) and Na−Hg (4.9 g, 21.9 mmol). The reaction mixture was stirred for 1 h at room temperature. Water (10 mL) and ether (20 mL) were added, and the supernatant was decanted. The residue was washed with ether (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc/hexane (1/1) as eluent gave the alcohol **51a** (1.2 g, 87%) as a white waxy solid: R_f = 0.4 (EtOAc/hexane 3:2); IR (neat) ν_{max}/cm^{-1} 3396, 2972, 1689 (NHC═O), 1424, 1114, 745; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 6.78 (q, J = 7.6 Hz, 1H), 6.62 (dd, J = 7.6, 2.7 Hz, 1H), 5.86 (d, J = 15.6 Hz, 1H), 5.57 (d, J = 15.6 Hz, 1H), 5.14 (s, 1H), 4.22−4.07 (m, 2H), 3.77−3.64 (m, 1H), 3.07 (q, J = 8.8 Hz, 1H), 2.28−2.23 (m, 2H), 1.95 (br s, 1H), 1.33−1.22 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz; rotamers) δ 155.1, 154.1 (NHC═O), 149.2, 148.9 (2 C), 137.7, 137.6 (CH), 130.4, 130.3 (2 C), 128.5, 128.3 (2 CH), 123.9, 123.8 (CH), 119.3, 119.0 (CH), 109.7, 109.6 (CH), 70.4, 70.4 (C), 61.3, 61.1 (CH_2), 46.0, 45.7 (CH_2), 35.5, 35.3 (CH_2), 29.6, 29.7 (2 CH_3), 14.8, 14.6 (CH_3); HRMS m/z calcd for $C_{18}H_{24}N_2O_3$ [M + H$^+$] 317.1900, found 317.1866.

*(E)-2-Methyl-4-(3-(2-(methylamino)ethyl)-1H-indol-2-yl)but-3-en-2-ol (**51**).* To a solution of the *N*-acetate tertiary alcohol **51a** (1 g, 3.16 mmol) in anhydrous THF (10 mL) was added $LiAlH_4$ (15.8 mL, 1.0 M solution, 15.8 mmol), and the mixture was stirred magnetically for 3 h at room temperature. The progress of the reaction was monitored by TLC until the starting **51a** had been completely consumed. Water (10 mL) was then added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1/9) as eluent furnished compound **51** (700 mg, 85%) as a yellow solid: R_f = 0.4 (MeOH/CH_2Cl_2 1.5/8.5); mp 101−103 °C; IR (neat) ν_{max}/cm^{-1} 3283, 2967, 2925, 1607, 1488, 1146, 1031, 750; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.03 (td, J = 7.6 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.74 (td, J = 7.3 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.93 (d, J = 15.6 Hz, 1H), 5.59 (d, J = 15.6 Hz, 1H), 4.51 (s, 1H), 4.24 (br s, 1H), 2.75−2.71 (ddd, J = 9.4, 5.8, 2.4 Hz, 1H), 2.64−2.59 (ddd, J = 8.8, 6.1, 2.7 Hz, 1H), 2.42 (s, 3H), 2.30−2.25 (ddd, J = 8.8, 7.0, 3.3 Hz, 1H), 2.04−2.00 (ddd, J = 9.7, 6.1, 3.6 Hz, 1H), 1.28 (d, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.1 (2 C), 136.5 (CH), 133.7 (2 C), 131.6 (CH), 127.7 (CH), 124.5 (CH), 118.8 (CH), 109.2 (CH), 70.4 (C), 52.2 (CH_2), 39.5 (CH_2), 36.7 (CH_3), 29.7 (2 CH_3); HRMS m/z calcd for $C_{16}H_{22}N_2O$ [M + H$^+$] 259.1800, found 259.1811.

*Isoborreverine (**5**).* To a solution of the alcohol **51** (100 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (5 mL) was added a catalytic amount of TFA (22 mg, 0.19 mmol), and the mixture was stirred magnetically for 30 min at room temperature. The progress of the reaction was monitored by TLC until the starting alcohol had been completely consumed. A saturated solution of $NaHCO_3$ (5 mL) was then added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH/CH_2Cl_2 (1.5/8.5) as eluent furnished isoborreverine (**5**; 80 mg, 86%) as a yellow solid: R_f = 0.3 (MeOH/CH_2Cl_2 1/9); mp 107−109 °C.

*Isoborreverine (**5**).* To a solution of the diene **43** (100 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (5 mL) was added a catalytic amount of TFA (24 mg, 0.20 mmol), and the mixture was stirred magnetically for 30 min at room temperature. The progress of the reaction was monitored by TLC until the starting diene **43** had been completely consumed. A saturated solution of $NaHCO_3$ (5 mL) was then added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using $MeOH/CH_2Cl_2$ (1.5/8.5) as eluent furnished isoborreverine (**5**; 20 mg, 20%) as a yellow solid: R_f = 0.3 ($MeOH/CH_2Cl_2$ 1/9). The data exactly matched those of isoborreverine (**5**) made earlier from compound **41**.

ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra for all compounds and a CIF file giving crystallographic data for compound **19b**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*D.H.D.: fax, (+91)-512-2596537; tel, (+91)-512-2597436; e-mail, ddethe@iitk.ac.in.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Petasis, N. A.; Zipkin, R. E.; Uenishi, J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1982**, *101*, 5555. (b) Luo, G.; Lin, L. S.; Corey, E. J. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (c) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (d) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393. (e) Torre, M. C. D. L.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160. (f) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (g) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757. (h) Zhang, W.; Luo, S.; Fang, F.; Chen, Q.; Hu, H.; Jia, X.; Zhai, H. *J. Am. Chem. Soc.* **2005**, *127*, 18. (i) Razzak, M.; De Brabander, J. K. *Nat. Chem. Biol.* **2011**, *7*, 865.

(2) (a) Midiwo, J. O.; Clough, J. M. In *Aspects of African Biodiversity, Proceedings of the Pan Africa Chemistry Network Biodiversity Conference*; Nairobi, Kenya, Sept 10−12, 2008; Midiwo, J. O., Clough, J. M., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2009; pp 11−19. (b) Kumar, N.; Sharma, M.; Rawat, D. S. *Curr. Med. Chem.* **2011**, *18*, 3889. (c) Fattorusso, E.; Taglialatela-Scafati, O. *Phytochem. Rev.* **2010**, *9*, 515. (d) Wells, T. N. *Malar. J.* **2011**, *10* (suppl. 1), S3.

(3) (a) Fernandez, L. S.; Jobling, M. F.; Andrews, K. T.; Avery, V. M. *Phytother. Res.* **2008**, *22*, 1409. (b) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329.

(4) Pousset, J.; Kerharo, J.; Maynart, G.; Monseur, X.; Cave, A.; Goutarel, R. *Phytochemistry* **1973**, *12*, 2308.

(5) Pousset, J. L.; Cave, A.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Chem. Commun.* **1977**, 261.

(6) Balde, A. M.; Pieters, L.; Gergely, A.; Wray, V.; Claeys, M.; Vlietinck, A. *Phytochemistry* **1991**, *30*, 997.

(7) Fernandez, L. S.; Sykes, M. L.; Andrews, K. T.; Avery, V. M. *Int. J. Antimicrob. Agents* **2010**, *36*, 275.

(8) (a) Tillequin, F.; Koch, M.; Pousset, J.-L.; Cave, A. *J. Chem. Soc., Chem. Commun.* **1978**, 826. (b) Tillequin, F.; Koch, M.; Rabaron, A. *J. Nat. Prod.* **1985**, *48*, 120. (c) Demaindreville, M.; Levy, J.; Tillequin, F.; Koch, M. *J. Nat. Prod.* **1983**, *46*, 310.

(9) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864.

(10) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706.

(11) (a) Vallakati, R.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 6936. (b) Vallakati, R.; May, J. A. *Synlett.* **2012**, *23*, 2577. (c) Vallakati, R.; Lundy, B. J.; Popova, S. J.; May, J. A. *Chirality* **2013**, DOI: 10.1002/chir.22134.

(12) Kumar, N. U.; Reddy, B. S.; Reddy, V. P.; Bandichhor, R. *Tetrahdron Lett.* **2012**, *53*, 4354.