Study on the NBS-Induced Rearrangement of 2-*tert*-Prenyltryptamines

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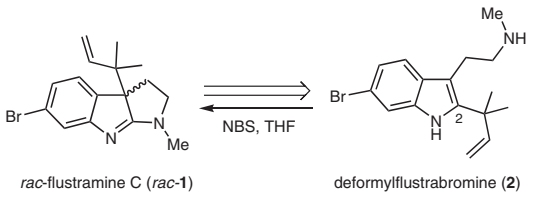
Received 20 April 2010

Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Abstract: Treatment of 2-*tert*-prenyltryptamines with *N*-bromosuccinimide gives clean access to the marine natural product flustramine C and analogues with the *tert*-prenyl group shifted to the 3a-position of the resulting pyrrolo[2,3-*b*]indole (70–80%). Dihydroflustramine C was obtained by DIBAL-H reduction of flustramine C. Bromination or N-methylation of the indole moiety does not influence the course of the rearrangement.

Key words: alkaloids, flustramines, indole, marine natural products, prenyl migration

Indole alkaloids functionalized with 1,1-dimethylallyl (*tert*-prenyl) moieties constitute an important group of natural products. In particular, the indole 3-position may be *tert*-prenylated. Examples from the marine environment include flustramine C (**1**) from the bryozoan *Flustra foliacea* (Scheme 1).[1]

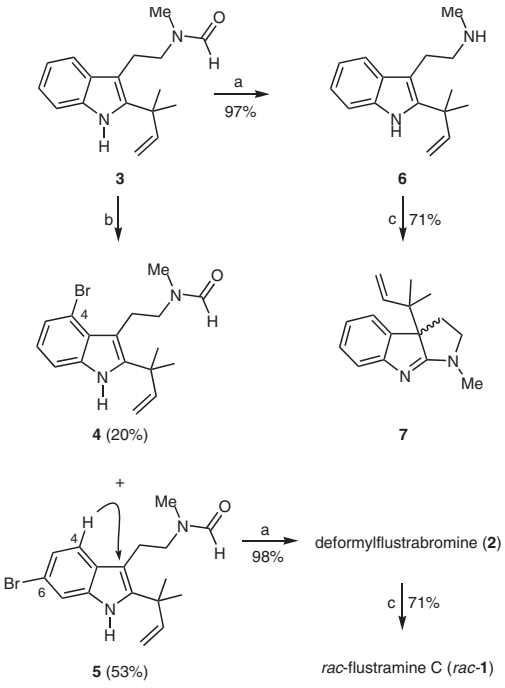


Scheme 1 Title reaction

In 2007, we reported that the 2-*tert*-prenylated natural product deformylflustrabromine (**2**)[2] can be converted to flustramine C (**1**) in one oxidative step employing *tert*-BuOCl/Et_3N via N-chlorination of the side chain, followed by cyclization and *tert*-prenyl shift.[3] Treatment of **2** with *N*-bromosuccinimide (NBS) in THF afforded *rac*-**1** in even higher yield. A related rearrangement affording 2-oxoindoles with a free 3-*tert*-prenyl group has been reported by Williams and co-workers, who used oxaziridines for oxidation and achieved the total synthesis of notoamide C[4] and versicolamide B.[5] Williams also showed that the biosynthesis of 3-*tert*-prenylated tryptophan derivatives can proceed via 2-*tert*-prenylated precursors, as in the case of the paraherquamides.[6]

Since regioselective introduction of *tert*-prenyl moieties at the indole nucleus is important for the synthesis of many tryptophan-derived natural products,[7] we investigated the scope of the facile NBS-induced oxidative cyclization/rearrangement.

Debromoflustrabromine (**3**, Scheme 2) was chosen as starting material, which was obtained in four steps from tryptamine by applying Danishefsky's *tert*-prenylation[8] to N_b-formyl-N_b-methyltryptamine.[3] After treatment with NBS in AcOH–HCO_2H (3:1),[9] the 6-brominated product **5** (53%) predominated over 4-bromoindole **4** (20%). In the ^1H NMR spectrum of **5** ($CDCl_3$), a doublet with a large coupling constant (J = 8.4 Hz) was observed for each of the rotamers (δ = 7.29, 7.49, respectively), which coupled with C-3 (δ = 107.1, 108.0, respectively) in the HMBC experiment. The doublets with the small coupling constant (J = 1.6 Hz, 7-H) did not couple with C-3.



Scheme 2 Two examples of sequential cyclization and 2,3-*tert*-prenyl transfer affording pyrrolo[2,3-*b*]indoles. *Reagents and conditions*: (a) aq 32% NaOH–EtOH (1:15), r.t., 48 h; (b) NBS (1 equiv), AcOH–HCO_2H (3:1), r.t., 30 min; (c) NBS (1 equiv), THF, 0 °C, 1 h.

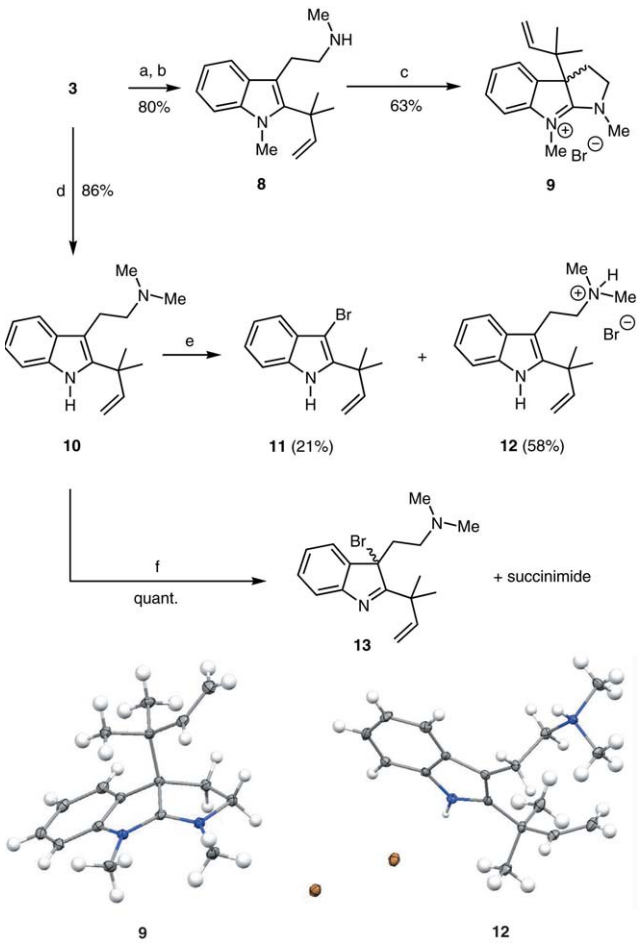
Probably, the indole 3-position is protonated in AcOH–HCO_2H (3:1) affording the indoleninium ion. S_EAr reaction will then be favored at the indole 4- and 6-positions, which are located at the *meta*-positions with respect to the

SYNTHESIS 2010, No. 13, pp 2161–2170
Advanced online publication: 02.06.2010
DOI: 10.1055/s-0029-1218811; Art ID: C02610SS

protonated iminium nitrogen and in the *ortho*- and *para*-positions of the indole 3-position.

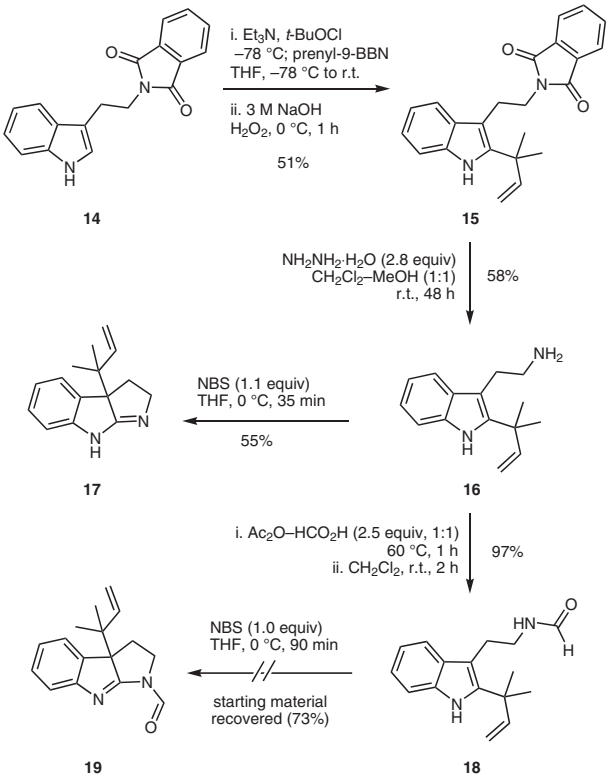
Alkaline hydrolysis of **5** and **3** afforded the 6-brominated deformylflustrabromine (**2**) and the nonbrominated secondary amine **6**, respectively (Scheme 2). On treatment of **2** and **6** with NBS (1 equiv) in THF at 0 °C, cyclization and *tert*-prenyl 2,3-migration took place affording pyrrolo[2,3-*b*]indoles **1** and **7** in yields of 71%. No side products were isolated. Since bromination of the benzene section of the indole did not influence the reaction, further reactions addressed nonbrominated substrates.

We wondered whether indole and side chain nitrogens could be methylated while still allowing cyclization and *tert*-prenyl migration. Indole-N_a-methylated compound **8** was obtained in two steps from **3**. N_b,N_b-Dimethyl-2-*tert*-prenyltryptamine **10** was obtained by DIBAL-H reduction of **3** (Scheme 3). We were pleased to observe that our NBS-induced cyclization-shift sequence also worked with N_a-methylindole **8** affording *N*,*N*′-dimethylamidinium salt **9**, which precipitated from EtOAc (63% yield). X-ray analysis clarified that bromide was the counterion. In the case of N_b,N_b-dimethyl-2-*tert*-prenyltryptamine **10**, oxidation with NBS was carried out in acetone for solubility reasons. After aqueous NaOH workup and chromatography on silica gel, we isolated 3-bromoindole **11** (21%, Scheme 3) and hydrobromide **12** (58%) as major products.



Scheme 3 Behavior of 2-*tert*-prenylated N_a-methyltryptamine **8** and of 2-*tert*-prenylated N_b,N_b-dimethyltryptamine **10**. *Reagents and conditions*: (a) i. NaH, DMF, 0 °C, 20 min, ii. MeI, r.t., 45 min; (b) aq 32% NaOH–EtOH (1:8), r.t., 48 h; (c) NBS (1 equiv), THF, 0 °C, 20 min; (d) DIBAL-H (1.9 equiv), THF, r.t., 24 h; (e) i. NBS (1 equiv), acetone, 0 °C, 50 min, ii. Et_2O, aq 2 M NaOH, iii. chromatography; (f) NBS (1 equiv), acetone-d_6, r.t., 45 min.

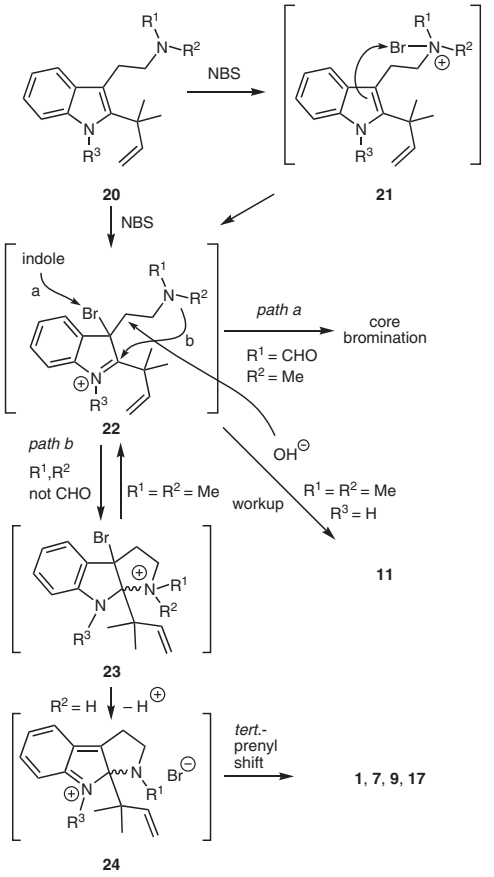
It was unclear whether the cyclization/rearrangement sequence would also occur in the absence of side-chain methylation (Scheme 4). For the synthesis of the free amine, we had to start from phthalimide protected tryptamine **14**, which underwent *tert*-prenylation at the indole 2-position affording **15**, and was subsequently hydrazinolyzed to **16**. NBS-induced cyclization/2-*tert*-prenyl shift again occurred, albeit in a somewhat lower yield (**17**, 55%). The monoformyl compound **18**, however, did not yield any isolable cyclization product; only starting material (73% after column chromatography) was recovered.



Scheme 4 Synthesis of 2-*tert*-prenyltryptamine (**16**) and its formylated analogue **18**, and their behavior on treatment with NBS in THF

Scheme 5 outlines our current interpretation of the results. We expect that the reaction sequence follows the order bromination, cyclization, *tert*-prenyl migration with competing pathways depending on side chain substitution. In the first step, the 3-bromoindolenine **22** is formed. In an NMR experiment in acetone-d_6 at room temperature (Scheme 3), we observed that N_b,N_b-dimethyl-2-*tert*-prenyltryptamine **10** was quantitatively converted to bromoindolenine **13** on addition of NBS (1 equiv). Succinimide accounted for the only other major signals.

Characteristically, the olefinic proton of the *tert*-prenyl group was shifted in the ^{1}H NMR spectrum from 6.19 to 6.55 ppm. In the ^{13}C NMR spectrum, a downfield-shifted signal at δ = 186.6 (indole C-2) indicated the presence of an imine carbon.



Scheme 5 Formation and reactions of a common 3-bromoindolenine intermediate **22**

Regarding the formation of the 3-bromoindolenines themselves, side chain N-bromination is likely to be the first step of the sequence for all starting materials with non-formylated side chains (**2**, **6**, and **8**). N-Halogenation of amines with NBS and NCS is possible,[10] and it has been reported that secondary amines catalyze bromination of aromatic compounds with NBS via *N*-bromoamines.[11] Side chain halogenation has also been observed when using *tert*-BuOCl.[3]

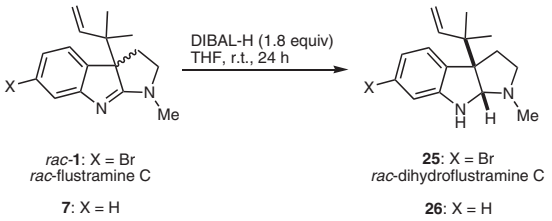
The 3-bromoindolenines are only converted into pyrrolo[2,3-*b*]indoles if the side chain is neither formylated nor dimethylated. In that case, tricyclic intermediate **23** is deprotonated and loses bromide affording an azaxylylene-type intermediate **24**. Prenyl shift then leads to indole-N-protonated or -alkylated flustramine C-type products **1**, **7**, **9**, and **17**.

In the case of N_b,N_b-dimethylation ($R^1 = R^2 = Me$), deprotonation of **23** is not possible and loss of bromide would generate an unlikely dication. On workup with sodium hydroxide, loss of the side chain of the 3-bromoindolenine can be explained by nucleophilic attack of hydroxide. We did not observe intramolecular formation of a dimethylaziridinium ion in acetone-d_6. Concomitant formation of hydrobromide **12** (Scheme 3) requires reduction of Br^+ to bromide, probably by disproportionation of hypobromite in aqueous sodium hydroxide during workup.

It has been shown that 3-bromoindoleninium ions such as **22** can brominate other indoles.[12] This reaction may be the fastest pathway if $R^1 = Me$ and $R^2 = CHO$ in THF (Scheme 5, path a), as in compound **3**.

In summary, our experiments indicate that the NBS-induced oxidative cyclization and rearrangement of 2-*tert*-prenyltryptamines with primary or secondary amine side chains is a robust reaction. 6-Bromination of the indole does not influence the outcome of the reaction, nor is the presence of the indole NH proton required.

Finally, *rac*-flustramine C (*rac*-**1**) was reduced diastereoselectively to *rac*-dihydroflustramine C (*rac*-**25**) with DIBAL-H in 93% yield (Scheme 6). Dihydroflustramine has been reported as a marine natural product.[13] Similarly, *rac*-debromodihydroflustramine C (**26**) was obtained from compound **7** (73%).



Scheme 6 DIBAL-H reduction to *rac*-dihydroflustramine C (**25**, 93%) and its debromo analogue **26** (73%).

NMR spectra were taken with a Bruker DRX-400 (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) and a Bruker AV III-400 (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) referenced to solvent signal or TMS. All measurements were carried out at 300 K. Mass spectra were obtained with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and a JMS-T100GC spectrometer coupled with an Agilent 6890 gas chromatograph. IR spectra were recorded with a Bruker Tensor 27 spectrometer. UV/Vis spectra were measured with a Varian Cary 100 Bio UV/Vis-spectrometer. Chemicals were purchased from commercial suppliers and used without further purification. Petroleum ether (PE) refers to the fraction boiling in the range 50–60 °C. Silica gel 60 (40–63 μm, Merck) and silica gel 200 (63–200 μm, Merck) were used for column chromatography.

***N*-{2-[6-Bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}-*N*-methylformamide (5) and *N*-{2-[4-Bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}-*N*-methylformamide (4)**

To a stirred solution of debromoflustrabromine (**3**; 3, 0.8 g, 2.98 mmol, 1.0 equiv) in AcOH–HCO_2H (24.1 mL, 3:1) was added a solution of NBS (0.6 g, 3.1 mmol, 1.0 equiv) in AcOH–HCO_2H (15 mL, 3:1). The solution was stirred at r.t. for 30 min, before it was added to a mixture of Et_2O (50 mL) and ice (50 g) and was diluted with Et_2O (100 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and aq 1 M NaOH (50 mL), washed again with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude solid was washed with MeOH (3 × 4 mL). Re-

maining solvent was removed under reduced pressure, followed by column chromatography (silica gel, PE–EtOAc, 1:1) affording flustrabromine **5** (0.55 g, 1.57 mmol, 53%) as a colorless solid; R_f = 0.43 (PE–EtOAc, 1:1); mp 218–220 °C.

IR (ATR): 3435 (m, br), 3087 (w), 3054 (w), 2972 (w), 2929 (w), 2872 (w), 1653 (s, br), 1463 (m, br), 1392 (m), 1334 (w), 1222 (m), 1164 (m), 1067 (w), 1043 (w), 995 (w), 909 (m), 863 (m), 804 (m), 784 (m), 728 (m), 695 (m), 661 (m), 633 (w), 620 (w), 590 (m), 539 cm^{-1} (w).

NMR: Ratio of rotamers in $CDCl_3$ = 1:0.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 8.21 (br s, 1 H, indole NH), 7.99 (s, 1 H, CHO), 7.49 (d, ^3J = 8.4 Hz, 1 H, indole 4-H), 7.46 (d, ^4J = 1.7 Hz, 1 H, indole 7-H), 7.20 (dd, ^4J = 1.7 Hz, ^3J = 8.4 Hz, 1 H, indole 5-H), 6.10 [dd, ^3J = 17.5, 10.4 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.21–5.15 [dd, ^3J = 17.5 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$)], 5.21–5.15 [dd, ^3J = 10.4 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.53–3.38 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.06–2.99 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 2.96 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.52 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) = 162.5 (CHO), 145.5 [CH_2=*C*H(CH_3)$_2$C], 140.9 (indole C-2), 135.0 (indole C-7a), 128.1 (indole C-3a), 122.9 (indole C-5), 119.9 (indole C-4), 115.0 (indole C-6), 113.7 (indole C-7), 112.4 [*C*H$_2$=CH(CH_3)$_2$C], 107.1 (indole C-3), 50.2 [CCH$_2$*C*H$_2$N(CH_3)CHO], 38.9 [NHC*C*(CH_3)$_2$CH=CH_2], 30.1 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 27.6 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 24.9 [C*C*H$_2$CH$_2$N(CH_3)CHO].

^{1}H NMR (400 MHz, $CDCl_3$): δ (minor) = 8.07 (br s, 1 H, indole NH), 8.00 (s, 1 H, CHO), 7.43 (d, ^4J = 1.3 Hz, 1 H, indole 7-H), 7.29 (d, ^3J = 8.4 Hz, 1 H, indole 4-H), 7.19 (dd, ^4J = 1.7 Hz, ^3J = 8.4 Hz, 1 H, indole 5-H), 6.13–6.08 [dd, ^3J = 17.6, 10.4 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.21–5.15 [dd, ^3J = 17.6 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.21–5.15 [dd, ^3J = 10.4 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.53–3.38 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.06–2.99 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 2.95 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.55 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor) = 162.5 (CHO), 145.5 [CH_2=*C*H(CH_3)$_2$C], 140.5 (indole C-2), 134.9 (indole C-7a), 128.5 (indole C-3a), 122.7 (indole C-5), 119.5 (indole C-4), 114.9 (indole C-6), 113.4 (indole C-7), 112.3 [*C*H$_2$=CH(CH_3)$_2$C], 108.0 (indole C-3), 45.5 [CCH$_2$*C*H$_2$N(CH_3)CHO], 39.0 [NHC*C*(CH_3)$_2$CH=CH_2], 35.1 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 27.6 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 22.6 [C*C*H$_2$CH$_2$N(CH_3)CHO].

MS (ESI): *m*/*z* (%) = 348 ([M]$^+$, 25), 289 ([M – C_5H_9]$^+$, 33), 276 ([M – C_3H_6NO]$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{21}{}^{79}BrN_2O$ [M]$^+$: 348.0837; found: 348.0838.

UV (MeCN): λ_{max} (lg ε) = 288 (3.85), 232 (4.58), 200 nm (4.41).

4-Bromoindole 4

Compound **4** was isolated by column chromatography (silica gel, eluent: PE–EtOAc, 1:1) from the above product mixture; yield: 20%; R_f = 0.58 (PE–EtOAc, 1:1); mp 155 °C (dec.).

IR (ATR): 3295 (m, br), 3081 (w), 3055 (w), 2970 (w), 2930 (w), 2872 (w), 1655 (s, br), 1463 (m, br), 1390 (m), 1333 (w), 1246 (w), 1223 (w), 1160 (m), 1067 (w), 1044 (w), 997 (w), 909 (m), 862 (w), 803 (m), 728 (m), 694 (m), 659 (w), 590 cm^{-1} (w).

NMR: Ratio of rotamers in $CDCl_3$: 1:0.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 8.13 (s, 1 H, CHO), 8.08 (br s, 1 H, indole NH), 7.21–7.17 (m, 2 H, indole 5-H, indole 7-H), 6.90 (dd, ^3J = 7.8 Hz, 1 H, indole 6-H), 6.06 [dd, ^3J = 17.4, 10.5 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.17 [dd, ^3J = 12.3 Hz, ^2J = 0.8 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.13 [dd, ^3J = 5.5 Hz, ^2J = 0.8 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.48–3.43 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.23–3.19 (m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 2.93 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.48 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) = 162.8 (CHO), 145.4 [CH_2=*C*H(CH_3)$_2$C], 141.6 (indole C-2), 135.5 (indole C-7a), 126.6 (indole C-3a), 124.6 (indole C-5), 122.4 (indole C-6), 113.0 (indole C-4), 112.4 [*C*H$_2$=CH(CH_3)$_2$C], 110.2 (indole C-7), 107.9 (indole C-3), 51.7 (CCH$_2$*C*H$_2$N(CH_3)CHO], 38.8 [CNHC*C*(CH_3)$_2$CH], 29.8 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 27.6 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 24.6 [C*C*H$_2$CH$_2$N(CH_3)CHO].

^{1}H NMR (400 MHz, $CDCl_3$): δ (minor) = 8.03 (br s, 1 H, indole NH), 8.00 (s, 1 H, CHO), 7.21–7.17 (m, 2 H, indole 5-H, indole 7-H), 6.87 (dd, ^3J = 7.8 Hz, 1 H, indole 6-H), 6.07 [dd, ^3J = 17.4, 10.5 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.15 [dd, ^3J = 8.4 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.11 [dd, ^3J = 2.2 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.58–3.54 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.23–3.19 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 3.02 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.55 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor) = 162.2 (CHO), 145.3 [CH_2=*C*H(CH_3)$_2$C], 142.2 (indole C-2), 135.5 (indole C-7a), 126.6 (indole C-3a), 124.4 (indole C-5), 122.0 (indole C-6), 112.7 (indole C-4), 112.4 [*C*H$_2$=CH(CH_3)$_2$C], 110.0 (indole C-7), 108.4 (indole C-3), 46.9 [CCH$_2$*C*H$_2$N(CH_3)CHO], 39.1 [CNHC*C*(CH_3)$_2$CH], 35.1 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 27.6 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 22.6 [C*C*H$_2$CH$_2$N(CH_3)CHO].

MS (EI, 70 eV): *m*/*z* (%) = 348 ([M]$^+$, 18), 289 ([M – C_5H_9]$^+$, 9), 276 ([M – C_3H_6NO]$^+$, 100).

GC-HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}{}^{79}BrN_2O$ [M]$^+$: 348.0832; found: 348.0826; *m*/*z* calcd for $C_{17}H_{21}{}^{81}BrN_2O$ [M]$^+$: 350.0811; found: 350.0809.

UV (MeCN): λ_{max} (lg ε) = 289 (3.86), 232 (4.56), 200 nm (4.41).

***N*-Methyl-2-[2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethanamine (6)**

To a solution of debromoflustrabromine (**3**; 1 g, 3.70 mmol, 1.0 equiv) in EtOH (150 mL) was added aq 32% NaOH (11 mL). The reaction mixture was refluxed for 48 h and cooled to r.t. H_2O (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with H_2O (4 × 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure affording **6** (870 mg, 3.59 mmol, 97%) as an orange oil.

IR (ATR): 3434 (w), 3298 (w, br), 3185 (w, br), 3080 (w), 3056 (w), 2967 (m), 2932 (w), 2870 (w), 2798 (w), 1632 (w), 1460 (m), 1360 (w), 1339 (w), 1303 (w), 1232 (w), 1129 (w), 1103 (w), 1008 (m), 914 (m), 738 (s), 597 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1 H, indole NH), 7.56 (dd, ^4J = 2.0 Hz, ^3J = 6.4 Hz, 1 H, indole 4-H), 7.30 (dd, ^4J = 2.2 Hz, ^3J = 6.6 Hz, 1 H, indole 7-H), 7.16–7.02 (m, 2 H, indole 5-H, 6-H), 6.13 [dd, ^3J = 17.4, 10.5 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.20–5.11 [m, 2 H, C*H*$_2$=CH(CH_3)$_2$C], 3.09–2.98 [m, 2 H, CH_3NHCH$_2$C*H*$_2$C], 2.89–2.81 (m, 2 H, CH_3NHC*H*$_2$CH$_2$C), 2.48 (s, 3 H, CH$_2$CH$_2$NHC*H*$_3$), 1.54 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C], 1.50 (br s, 1 H, CCH$_2$CH$_2$N*H*CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0 [CH_2=*C*H(CH_3)$_2$C], 139.5 (indole C-2), 134.1 (indole C-7a), 129.8 (indole C-3a), 121.3 (indole C-6), 119.1 (indole C-5), 118.3 (indole C-4), 111.9 [*C*H$_2$=CH(CH_3)$_2$C], 110.3 (indole C-7), 109.0 (indole C-3), 53.1 (CH$_2$*C*H$_2$NHCH$_3$), 39.0 [NHC*C*(CH_3)$_2$CH], 36.5 (CH$_2$CH$_2$NH*C*H$_3$), 27.7 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 25.6 (C*C*H$_2$CH$_2$NHCH$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 242 ([M]$^+$, 5), 199 (100), 184 ([M – C_3H_8N]$^+$, 83), 172 ([M – C_5H_9]$^+$, 7), 168 (44).

GC-HRMS (EI): *m/z* calcd for $C_{16}H_{22}N_2$ [M]$^+$: 242.1778; found: 242.1758.

UV ($CHCl_3$): λ_{max} (lg ε) = 283 (3.86), 239 (3.98), 233 nm (3.79).

rac-Debromoflustramine C (7)

To a solution of debromodeformylflustrabromine (**6**; 200 mg, 0.83 mmol, 1.0 equiv) in THF (20 mL) was added NBS (147 mg, 0.83 mmol, 1.0 equiv). The reaction mixture was stirred at 0 °C for 1 h and diluted with Et_2O (50 mL). The organic layer was washed with aq 2 N NaOH (3 × 50 mL) and H_2O (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc) affording *rac*-debromoflustramine C (**7**; 156 mg, 0.61 mmol, 71%) as a colorless oil; R_f = 0.2 (EtOAc).

IR (ATR): 3059 (w), 2969 (w), 2930 (w), 2877 (w), 2796 (w), 1633 (s), 1576 (s), 1446 (m), 1412 (m), 1380 (w), 1364 (w), 1307 (w), 1278 (m), 1216 (m), 1181 (m), 1154 (w), 1103 (w), 1007 (w), 987 (w), 915 (m), 848 (w), 818 (w), 765 (s), 747 (s), 685 (w), 656 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (dt, ^4J = 1.3 Hz, ^3J = 7.6 Hz, 1 H, 6-H), 7.11 (dd, ^4J = 0.8 Hz, ^3J = 7.8 Hz, 1 H, 5-H), 7.09–7.07 (m, 1 H, 4-H), 6.80 (dt, ^4J = 1.2 Hz, ^3J = 7.4 Hz, 1 H, 7-H), 6.08–6.01 [m, 1 H, CH_2=C*H*$(CH_3)_2$C], 5.07 [s, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_Z$], 5.04 [dd, ^3J = 7.0 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_E$], 3.95 [ddd, ^3J = 6.3, 3.9 Hz, ^2J = 12.7 Hz, 1 H, (CH_3)NC*H*$_2$CH$_2$C], 3.40 [dt, ^3J = 10.1, 1.0 Hz, 1 H, (CH_3)NC*H*$_2$CH$_2$C], 3.05 (s, 3 H, NCH_3), 2.39 [ddd, ^3J = 6.1, 0.7 Hz, ^2J = 13.1 Hz, 1 H, (CH_3)NCH$_2$C*H*$_2$C], 2.11 [ddd, ^3J = 7.7, 5.8 Hz, ^2J = 16.0 Hz, 1 H, (CH_3)NCH$_2$C*H*$_2$C], 1.01 [s, 3 H, CH_2=CH(C*H*$_3)_2$C], 0.87 [s, 3 H, CH_2=CH(C*H*$_3)_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.0 (C-8a), 160.8 (C-7a), 143.7 [CH_2=*C*H$(CH_3)_2$C], 138.2 (C-3b), 128.5 (C-6), 123.5 (C-4), 119.6 (C-7), 115.7 (C-5), 113.3 [*C*H$_2$=CH$(CH_3)_2$C], 66.1 (C-3a), 59.9 (C-2), 43.1 [N=CC*C*$(CH_3)_2$CH=CH$_2$], 33.4 (NCH_3), 27.9 (C-3), 22.8 [CH_2=CH(*C*H$_3)_2$C], 21.6 [CH_2=CH(*C*H$_3)_2$C].

MS (EI, 70 eV): *m/z* (%) = 240 ([M]$^+$, 15), 172 ([M – C_5H_9 + H]$^+$), (30), 171 ([M – C_5H_9]$^+$, 100), 130 (30).

GC-HRMS (EI): *m/z* calcd for $C_{16}H_{20}N_2$ [M]$^+$: 240.1621; found: 240.1638.

UV ($CHCl_3$): λ_{max} (lg ε) = 283 (3.83), 239 (3.62), 231 nm (3.55).

N-Methyl-*N*-{2-[1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}formamide

NaH (60% suspension in mineral oil, 222 mg, 5.552 mmol, 1.5 equiv) was washed with pentane (5 mL) and dried under high vacuum. At 0 °C under Ar, a solution of debromoflustrabromine (**3**; 1.0 g, 3.701 mmol, 1.0 equiv) in DMF (30 mL) was added. After 30 min at 0 °C, a solution of MeI (580 mg, 4.072 mmol, 1.1 equiv) in DMF (10 mL) was added dropwise, and the reaction mixture was stirred at r.t. for 45 min. H_2O (40 mL) was added cautiously and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the pure title compound (1.04 g, 3.66 mmol, 99%) as a yellow oil.

IR (ATR): 3050 (w), 2970 (w), 2930 (w), 2873 (w), 1669 (s), 1474 (m), 1383 (m), 1355 (m), 1320 (w), 1232 (w), 1177 (w), 1148 (w), 1081 (m), 1015 (w), 995 (w), 913 (m), 741 (s), 562 cm^{-1} (w).

NMR: Ratio of rotamers in $CDCl_3$ = 1.7:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) = 8.02 (s, 1 H, CHO), 7.47 (d, ^3J = 7.0 Hz, 1 H, indole 4-H), 7.26–7.18 (m, 2 H, indole 6-H, indole 7-H), 7.14–7.01 (m, 1 H, indole 5-H), 6.17 [dd, ^3J = 17.5, 10.5 Hz, 1 H, CH_2=C*H*$(CH_3)_2$C], 5.10 [dd, ^3J = 10.6 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_Z$], 4.99 [t, ^3J = 1.0 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_E$], 3.72 [s, 3 H, CN(C*H*$_3$)C], 3.45–3.41 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.24–3.19 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 2.98 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.62 [s, 6 H, CH_2=CH(C*H*$_3)_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) = 162.5 (CHO), 147.4 [CH_2=*C*H$(CH_3)_2$C], 140.7 (indole C-2), 137.7 (indole C-7a), 128.1 (indole C-3a), 121.8 (indole C-6), 119.3 (indole C-5), 117.4 (indole C-4), 112.1 [*C*H$_2$=CH$(CH_3)_2$C], 108.9 (indole C-7), 107.6 (indole C-3), 51.3 [CCH$_2$*C*H$_2$N(CH_3)CHO], 40.7 [CN(CH_3)C*C*$(CH_3)_2$CH], 33.2 [CHCN(*C*H$_3$)C], 30.1 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 29.4 [2 C, CH_2=CH(*C*H$_3)_2$C], 25.5 [C*C*H$_2$CH$_2$N(CH_3)CHO].

^{1}H NMR (400 MHz, $CDCl_3$): δ (minor) = 8.06 (s, 1 H, CHO), 7.64 (d, ^3J = 7.0 Hz, 1 H, indole 4-H), 7.26–7.18 (m, 2 H, indole 6-H, indole 7-H), 7.14–7.01 (m, 1 H, indole 5-H), 6.18 [dd, ^3J = 17.5, 10.6 Hz, 1 H, CH_2=C*H*$(CH_3)_2$C], 5.09 [dd, ^3J = 10.6 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_Z$], 4.94 [t, ^3J = 1.0 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_E$], 3.71 [s, 3 H, CN(C*H*$_3$)C], 3.52–3.48 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)CHO], 3.24–3.19 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)CHO], 2.96 [s, 3 H, CCH$_2$CH$_2$N(C*H*$_3$)CHO], 1.66 [s, 6 H, CH_2=CH(C*H*$_3)_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor) = 162.4 (CHO), 147.7 [CH_2=*C*H$(CH_3)_2$C], 140.6 (indole C-2), 137.6 (indole C-7a), 128.5 (indole C-3a), 121.6 (indole C-6), 119.1 (indole C-5), 118.0 (indole C-4), 111.9 [*C*H$_2$=CH$(CH_3)_2$C], 108.6 (indole C-7), 108.4 (indole C-3), 46.6 [CCH$_2$*C*H$_2$N(CH_3)CHO], 40.8 [CN(CH_3)C*C*$(CH_3)_2$CH], 35.1 [CCH$_2$CH$_2$N(*C*H$_3$)CHO], 33.2 [CHCN(*C*H$_3$)C], 29.5 [2 C, CH_2=CH(*C*H$_3)_2$C], 23.1 [C*C*H$_2$CH$_2$N(CH_3)CHO].

MS (EI, 70 eV): *m/z* (%) = 284([M]$^+$, 20), 212 ([M – C_3H_6NO]$^+$, 100), 198 ([M – C_4H_8NO]$^+$, 10), 182 (55).

GC-HRMS (EI): *m/z* calcd for $C_{18}H_{24}N_2O$ [M]$^+$: 284.1883; found: 284.1859.

UV ($CHCl_3$): λ_{max} (lg ε) = 290 (3.84), 240 nm (4.09).

N-Methyl-2-[1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethanamine (8)

To a solution of *N*-methyl-*N*-{2-[1-methyl-2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}formamide (600 mg, 2.11 mmol, 1.0 equiv) in EtOH (80 mL) was added aq 32% NaOH (8 mL). The reaction mixture was refluxed for 48 h and cooled to r.t. H_2O (50 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL), washed with H_2O (4 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure affording the pure title compound **8** (436 mg, 1.702 mmol, 81%) as a yellow oil.

IR (ATR): 3314 (w, br), 3050 (w), 2968 (w), 2933 (w), 2880 (w), 2791 (w), 1472 (s), 1355 (m), 1319 (m), 1233 (m), 1131 (w), 1109 (w), 1085 (w), 1015 (w), 995 (w), 912 (m), 739 (s), 707 (m), 686 (w), 562 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dt, ^4J = 0.8 Hz, ^3J = 7.8 Hz, 1 H, indole 4-H), 7.23–7.17 (m, 2 H, indole 6-H, indole 7-H), 7.09 (dd, ^4J = 1.6 Hz, ^3J = 6.4 Hz, 1 H, indole 5-H), 6.17 [dd, ^3J = 17.5, 10.6 Hz, 1 H, CH_2=C*H*$(CH_3)_2$C], 5.07 [dd, ^3J = 10.6 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_Z$], 4.95 [dd, ^3J = 17.5 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH$(CH_3)_2$C-H$_E$], 3.70 [s, 3 H, CN(C*H*$_3$)C], 3.19 (t, ^3J = 7.7 Hz, 2 H, CH_3NHCH$_2$C*H*$_2$C], 2.83 (t, ^3J = 7.7 Hz, 2 H, CH_3NHC*H*$_2$CH$_2$C), 2.47 (s, 3 H, CH$_2$CH$_2$NHC*H*$_3$), 1.70 (br s, 1 H, CH$_2$CH$_2$N*H*CH$_3$), 1.63 [s, 6 H, CH_2=CH(C*H*$_3)_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9 [CH_2=*C*H$(CH_3)_2$C], 140.2 (indole C-2), 137.6 (indole C-7a), 128.8 (indole C-3a), 121.5 (indole C-6), 118.9 (indole C-5), 118.2 (indole C-4), 111.8 [*C*H$_2$=CH$(CH_3)_2$C], 109.8 (indole C-3), 108.5 (indole C-7), 54.3 (CH$_2$*C*H$_2$NHCH$_3$), 40.8 [N(CH_3)C*C*$(CH_3)_2$CH], 36.5 (CH$_2$CH$_2$NH*C*H$_3$), 33.2 [CHCN(*C*H$_3$)CC], 29.6 [2 C, CH_2=CH(*C*H$_3)_2$C], 25.9 (C*C*H$_2$CH$_2$NHCH$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M]$^+$, 6), 213 ([M – C_2H_5N + H]$^+$, 100), 212 ([M – C_2H_5N]$^+$, 64), 199 (10), 198 ([M – C_3H_8N]$^+$, 70), 182 (35).

GC-HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_2$ [M]$^+$: 256.1934; found: 256.1961.

UV ($CHCl_3$): λ_{max} (lg ε) = 290 (3.84), 240 (4.10), 232 nm (3.75).

1,8-Dimethyl-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indolium Bromide (9)

To a solution of **8** (233 mg, 0.91 mmol, 1.0 equiv) in THF (16 mL) at 0 °C was added NBS (165 mg, 0.91 mmol, 1.0 equiv). After 20 min, the precipitate that had formed was washed with EtOAc (20 mL) and dried in vacuo to afford compound **9** (192 mg, 0.57 mmol, 63%) as a colorless amorphous solid; mp 166 °C.

IR (ATR): 3403 (w, br), 3328 (w), 3157 (w), 3080 (w), 3030 (w), 3006 (w), 2960 (w), 2895 (w), 2797 (w), 1772 (w), 1691 (s), 1608 (m), 1456 (m), 1433 (m), 1402 (m), 1373 (m), 1348 (w), 1329 (m), 1294 (m), 1178 (m), 1151 (m), 1105 (m), 1005 (w), 933 (m), 811 (m), 775 (s), 709 (w), 639 cm^{-1} (m).

^{1}H NMR (400 MHz, D_2O): δ = 7.58 (dt, ^4J = 1.3 Hz, ^3J = 7.9 Hz, 1 H, 6-H), 7.42 (dd, ^4J = 1.2 Hz, ^3J = 7.6 Hz, 1 H, 4-H), 7.32–7.27 (m, 2 H, 5-H, 7-H), 6.03 [dd, ^3J = 17.4, 10.8 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.26 [dd, ^3J = 10.8 Hz, ^2J = 0.8 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.21 [dd, ^3J = 17.4 Hz, ^2J = 0.8 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 4.56 [ddd, ^3J = 6.3, 9.5 Hz, ^2J = 11.7 Hz, 1 H, =CN(CH_3)C*H*$_2$CH$_2$C], 4.16 [ddd, ^3J = 11.5, 10.1 Hz, 1 H, =CN(CH_3)C*H*$_2$CH$_2$C], 3.83 [s, 3 H, CN$^+$(C*H*$_3$)=CN(CH_3)], 3.72 [s, 3 H, CN$^+$(CH_3)=CN(C*H*$_3$)], 2.79 [dd, ^3J = 6.0 Hz, ^2J = 13.4, 1 H, N(CH_3)CH$_2$C*H*$_2$C], 2.49 [dt, ^3J = 9.7, 3.6 Hz, ^2J = 13.3 Hz, 1 H, N(CH_3)CH$_2$C*H*$_2$C], 1.14 [s, 3 H, CH_2=CH(C*H*$_3$)$_2$C), 0.96 [s, 3 H, CH_2 CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, D_2O): δ = 180.9 (C-8a), 152.0 (C-7a), 144.6 [CH_2=*C*H(CH_3)$_2$C], 134.4 (C-3b), 132.5 (C-6), 127.9 (C-4), 126.8 (C-7), 118.7 [*C*H$_2$=CH(CH_3)$_2$C], 113.3 (C-5), 71.8 (C-3a), 68.0 (C-2), 48.8 [N$^+$(CH_3)=CC*C*(CH_3)$_2$CH=CH_2], 38.0 [N$^+$(CH_3)=CN(*C*H$_3$)CH$_2$], 34.0 [N$^+$(*C*H$_3$)=CN(CH_3)CH$_2$], 30.0 [C*C*H$_2$CH$_2$N(CH_3)C], 25.8 [CH_2=CH(*C*H$_3$)$_2$C], 24.7 [CH_2=CH(*C*H$_3$)$_2$C].

MS (ESI): *m*/*z* (%) = 255 ([M]$^+$, 100), 186 ([M – C_5H_9]$^+$, 16), 185 (5).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{23}N_2^+$ [M]$^+$: 255.1856; found: 255.1855.

UV (DMSO): λ_{max} (lg ε) = 296 (3.39), 275 (3.55), 253 nm (3.51).

***N*,*N*-Dimethyl-2-[2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethanamine (10)**

At r.t., DIBAL-H (17% in toluene, 6.22 mL, 6.218 mmol, 4.2 equiv) was added dropwise to a solution of debromoflustrabromine (**3**; 400 mg, 1.48 mmol, 1.0 equiv) in THF (10 mL) under argon. After 24 h, the reaction mixture was added in portions to ice water (150 mL). Aq 12 M HCl (10 mL) was added at 0 °C (pH 2) and the organic layer was extracted with Et_2O (3 × 30 mL). The aqueous layer was brought to pH 11 by addition of aq 12 M NaOH (12 M, 20 mL) and was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo to afford compound **10** (325 mg, 1.27 mmol, 86%) as a colorless oil.

IR (ATR): 3434 (w), 3255 (w, br), 3055 (w), 2968 (m), 2936 (m), 2867 (w), 2828 (w), 2789 (w), 1638 (w), 1459 (s), 1360 (w), 1341 (w), 1302 (w), 1247 (w), 1229 (w), 1137 (w), 1098 (w), 1029 (m), 1008 (m), 736 (s), 597 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (br s, 1 H, indole NH), 7.53 (d, ^3J = 7.5 Hz, 1 H, indole 4-H), 7.27 (dd, ^4J = 1.2 Hz, ^3J = 7.6 Hz, 1 H, indole 7-H), 7.12 (dt, ^4J = 1.4 Hz, ^3J = 7.5 Hz, 1 H, indole 6-H), 7.07 (dt, ^4J = 1.2 Hz, ^3J = 7.4 Hz, 1 H, indole 5-H), 6.13 [dd, ^3J = 17.4, 10.6 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.17 [dd, ^3J = 17.4 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.15 [dd, ^3J = 10.5 Hz, ^2J = 1.1 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.04–3.00 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)$_2$], 2.56–2.47 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)$_2$], 2.35 [s, 6 H, CCH$_2$CH$_2$N(C*H*$_3$)$_2$], 1.54 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9 [CH_2=*C*H(CH_3)$_2$C], 139.3 (indole C-2), 134.2 (indole C-7a), 129.7 (indole C-3a), 121.3 (indole C-6), 119.2 (indole C-5), 118.1 (indole C-4), 112.0 [*C*H$_2$=CH(CH_3)$_2$C], 110.4 (indole C-7), 108.9 (indole C-3), 60.4 [CCH$_2$*C*H$_2$N(CH_3)$_2$], 45.5 [2 C, CCH$_2$CH$_2$N(*C*H$_3$)$_2$], 38.9 [NHC*C*(CH_3)$_2$CH], 27.7 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 23.4 [C*C*H$_2$CH$_2$N(CH_3)$_2$].

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M]$^+$, 7), 198 ([M – C_3H_8N]$^+$, 10), 183 ([M – $C_4H_{10}N$ + H]$^+$, 10), 58 (100).

GC-HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_2$ [M]$^+$: 256.1934; found: 256.1944.

UV ($CHCl_3$): λ_{max} (lg ε) = 284 (3.87), 240 nm (3.99).

3-Bromo-2-(2-methylbut-3-en-2-yl)-1*H*-indole (11)

To a solution of *N*$_b$,*N*$_b$-dimethyl-2-*tert*-prenyltryptamine **10** (400 mg, 1.56 mmol, 1.0 equiv) in acetone (20 mL) was added NBS (308 mg, 1.72 mmol, 1.1 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 50 min and diluted with Et_2O (100 mL). The Et_2O layer was separated, washed with aq 2 M NaOH (2 × 50 mL), followed by H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 9:1) to afford compound **11** (88 mg, 0.33 mmol, 21%) as a dark green oil and compound **12** (305 mg, 0.91 mmol, 58%) as a yellow oil.

3-Bromoindole 11

R_f = 0.73 (acetone–PE, 1:2).

IR (ATR): 3151 (w, br), 3059 (w, br), 2964 (m), 2925 (m), 1704 (w), 1641 (w), 1617 (m), 1455 (m), 1385 (w), 1363 (w), 1259 (w), 1211 (w), 1101 (m), 1011 (m), 913 (w), 802 (m), 746 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (br s, 1 H, indole NH), 7.55–7.50 (m, 1 H, indole 4-H), 7.30–7.26 (m, 1 H, indole 7-H), 7.20–7.13 (m, 2 H, indole 5-H, indole 6-H), 6.17 [dd, ^3J = 17.4, 10.6 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.24 [dd, ^3J = 7.0 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.21 [dd, ^3J = 13.4 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 1.63 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3 [CH_2=*C*H(CH_3)$_2$C], 139.5 (indole C-2), 133.3 (indole C-7a), 129.0 (indole C-3a), 122.5 (indole C-6), 120.4 (indole C-5), 118.6 (indole C-4), 113.5 [*C*H$_2$=CH(CH_3)$_2$C], 110.7 (indole C-7), 87.9 (indole C-3), 39.0 [NHC*C*(CH_3)$_2$CH], 26.4 [2 C, CH_2=CH(*C*H$_3$)$_2$C].

MS (EI, 70 eV): *m*/*z* (%) = 263 ([M]$^+$, 24), 169 (100), 167 (18), 127 (31).

GC-HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}{}^{79}BrN_2$ [M]$^+$: 263.0304; found: 263.0295.

UV ($CHCl_3$): λ_{max} (lg ε) = 279 (3.86), 272 (3.87), 240 nm (4.00).

Hydrobromide 12

R_f = 0.49 (acetone–PE, 1:2).

IR (ATR): 3270 (w, br), 2966 (w, br), 2666 (w, br), 2462 (w), 1469 (s), 1342 (w), 1307 (w), 1236 (w), 1008 (m), 956 (m), 918 (m), 744 (s), 716 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br s, 1 H, indole NH), 7.57 (d, ^3J = 7.6 Hz, 1 H, indole 4-H), 7.35 (dd, ^4J = 1.3 Hz, ^3J = 7.5 Hz, 1 H, indole 7-H), 7.14 (dt, ^4J = 1.4 Hz, ^3J = 7.5 Hz, 1 H, indole 6-H), 7.09 (dt, ^4J = 1.2 Hz, ^3J = 7.4 Hz, 1 H, indole 5-H), 6.10 [dd,

^3J = 17.5, 10.5 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.17 [dd, ^3J = 14.4 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.15 [dd, ^3J = 7.4 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 3.32–3.28 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)$_2$], 3.00–2.96 [m, 2 H, CCH$_2$C*H*$_2$N(CH_3)$_2$], 2.72 [s, 6 H, CCH$_2$CH$_2$N(C*H*$_3$)$_2$], 1.54 [s, 6 H, CH$_2$=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6 [CH_2=*C*H(CH_3)$_2$C], 140.3 (indole C-2), 134.2 (indole C-7a), 128.8 (indole C-3a), 121.7 (indole C-6), 119.7 (indole C-5), 117.7 (indole C-4), 112.2 [*C*H$_2$=CH(CH_3)$_2$C], 110.8 (indole C-7), 105.2 (indole C-3), 58.2 [CCH$_2$*C*H$_2$N(CH_3)$_2$], 43.3 [2 C, CCH$_2$CH$_2$N(*C*H$_3$)$_2$], 38.8 [NHC*C*(CH_3)$_2$CH], 27.7 [2 C, CH$_2$=CH(*C*H$_3$)$_2$C], 20.9 [C*C*H$_2$CH$_2$N(CH_3)$_2$].

MS (ESI): *m*/*z* (%) = 257 ([M]$^+$, 67), 212 ([M – C_2H_7N]$^+$, 100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{25}N_2$ [M]$^+$: 257.2012; found: 257.2011.

UV (CH_2Cl_2): λ_{max} (lg ε) = 282 (3.86), 239 (3.91), 233 nm (3.68).

2-[3-Bromo-2-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl]-*N*,*N*-dimethylethanamine (13, NMR Experiment)

To a solution of **10** (60 mg, 0.23 mmol, 1.0 equiv) in acetone-d_6 (0.6 mL) in an NMR tube was added NBS (42 mg, 0.23 mmol, 1.0 equiv) at r.t. The NMR tube was shaken for 5 min and after 25 min, the NMR spectra were recorded.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.53 (d, ^3J = 7.4 Hz, 1 H, indole 4-H), 7.47 (d, ^3J = 6.7 Hz, 1 H, indole 7-H), 7.38 (dt, ^4J = 1.2 Hz, ^3J = 7.6 Hz, 1 H, indole 6-H), 7.30 (dt, ^4J = 1.1 Hz, ^3J = 7.4 Hz, 1 H, indole 5-H), 6.55 [dd, ^3J = 17.5, 10.7 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.30 [d, ^3J = 17.5 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 5.19 [d, ^3J = 10.6 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 2.88–2.75 [m, 2 H, CC*H*$_2$CH$_2$N(CH_3)$_2$], 2.68 [s, 4 H, (C*H*$_2$CO)$_2$NH], 2.01 [s, 6 H, CCH$_2$CH$_2$N(C*H*$_3$)$_2$], 1.97–1.88 [m, 1 H, CCH$_2$C*H*$_2$N(CH_3)$_2$], 1.71–1.65 [m, 1 H, CCH$_2$C*H*$_2$N(CH_3)$_2$], 1.67 [s, 3 H, CH_2=CH(C*H*$_3$)$_2$C], 1.62 [s, 3 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, acetone-d_6): δ = 186.6 (indole C-2), 179.0 [2 C, (CH_2*C*O)$_2$NH], 151.9 (indole C-7a), 145.0 (CH_2=*C*H(CH_3)$_2$C), 141.2 (indole C-3a), 130.5 (indole C-6), 127.6 (indole C-5), 123.3 (indole C-4), 121.3 (indole C-7), 113.5 [*C*H$_2$=CH(CH_3)$_2$C], 63.9 (indole C-3), 54.9 [CCH$_2$*C*H$_2$N(CH_3)$_2$], 45.1 [2 C, CCH$_2$CH$_2$N(*C*H$_3$)$_2$], 44.3 [N=C*C*(CH_3)$_2$CH=CH$_2$], 37.8 [C*C*H$_2$CH$_2$N(CH_3)$_2$], 30.2 [2 C, (*C*H$_2$CO)$_2$NH], 29.6 [CH_2=CH(*C*H$_3$)$_2$C], 27.7 [CH_2=CH(*C*H$_3$)$_2$C].

2-[2-(1*H*-indol-3-yl)ethyl]isoindoline-1,3-dione (14)

Phthalic anhydride (4.03 g, 27.0 mmol, 1.1 equiv) was added to a solution of tryptamine (3.9 g, 24.33 mmol, 1.0 equiv) in toluene (50 mL), followed by addition of Et_3N (3.75 mL, 27.0 mmol, 1.1 equiv). The reaction mixture was refluxed at 125 °C for 8 h, cooled to r.t. and added to ice water (100 mL). The yellow precipitate was recrystallized from MeOH (5 mL of MeOH/g) to obtain compound **14** (5.52 g, 19.01 mmol, 77%) as a brown solid; mp 164–166 °C.

IR (ATR): 3379 (m), 3352 (br, m), 3043 (w), 2979 (w), 2861 (w), 1767 (m), 1696 (s, br), 1617 (m), 1460 (m), 1430 (m), 1395 (s), 1355 (m), 1327 (m), 1230 (m), 1186 (w), 1169 (w), 1097 (m), 1058 (m), 1011 (w), 985 (m), 867 (m), 821 (w), 741 (s), 707 (s), 654 (m), 632 (m), 586 (m), 529 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br s, 1 H, indole NH), 7.82 [dd, ^3J = 5.8, 3.2 Hz, 2 H, N(C(=O)CC*H*CH)$_2$], 7.73 (d, ^3J = 8.32 Hz, 1 H, indole 4-H), 7.69 [dd, ^3J = 5.8, 3.1 Hz, 2 H, N(C(=O)CCHC*H*)$_2$], 7.34 (d, ^3J = 7.8 Hz, 1 H, indole 7-H), 7.17 (ddd, ^3J = 13.7, 6.1 Hz, ^2J = 1.3 Hz, 1 H, indole 6-H), 7.10 (dd, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1 H, indole 5-H), 7.08 (s, 1 H, indole 2-H), 4.00 (t, ^3J = 7.8 Hz, 2 H, CCH$_2$C*H*$_2$N), 3.15 (t, ^3J = 7.8 Hz, 2 H, CC*H*$_2$CH$_2$N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 [2 C, N(*C*(=O)CCHCH)$_2$], 136.2 (indole C-7a), 133.8 [2 C, N(C(=O)CCH*C*H)$_2$], 132.2 [2 C, N(C(=O)*C*CHCH)$_2$], 127.4 (indole C-3a), 123.2 [2 C, N(C(=O)C*C*HCH)$_2$], 122.1 (indole C-6), 122.0 (indole C-2), 119.5 (indole C-5), 118.9 (indole C-4), 112.5 (indole C-3), 111.1 (indole C-7), 38.5 (CNHCHCCH$_2$*C*H$_2$N), 24.5 (CNHCHC*C*H$_2$CH$_2$N).

MS (EI, 70 eV): *m*/*z* (%) = 290 ([M]$^+$, 29), 143 (36), 130 ([M – $C_9H_6NO_2$]$^+$, 100), 77 (11).

GC-HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}N_2O_2$ [M]$^+$: 290.1050; found: 290.1071.

UV (MeCN): λ_{max} (lg ε) = 354 (2.28), 289 (3.80), 281 (3.84), 240 (4.10), 220 (4.84), 194 nm (4.49).

2-{2-[2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}isoindoline-1,3-dione (15)

To a solution of **14** (2.2 g, 7.58 mmol, 1.0 equiv) in THF (45 mL) and Et_3N (1.4 mL, 10.34 mmol, 1.2 equiv) was added *t*-BuOCl[14] (1.17 mL, 10.34 mmol, 1.2 equiv) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C, before a freshly prepared solution of prenyl-9-BBN (0.5 M, 34.5 mL, 17.24 mmol, 2.0 equiv)[15] in THF was added dropwise. After 30 min, the mixture was allowed to warm to r.t. and was stirred for 1 h. Aq 3 M NaOH (18 mL) and H_2O_2 (30%, 18 mL) were added dropwise. The reaction mixture was stirred at r.t. for 1 h and diluted with Et_2O (200 mL). The organic layer was washed with brine–H_2O (1:1, 3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual yellow oil was recrystallized from $CHCl_3$–hexane (1:5, 30 mL) to afford compound **15** (1.37 g, 3.83 mmol, 50%) as a yellow amorphous solid; mp 143–146 °C.

IR (ATR): 3355 (m), 3084 (w), 3031 (w), 2970 (w), 2936 (w), 2867 (w), 1766 (w), 1696 (s), 1463 (m), 1430 (w), 1394 (s), 1354 (m), 1336 (m), 1245 (w), 1170 (w), 1103 (m), 1017 (m), 920 (m), 898 (w), 871 (m), 747 (s), 714 (s, br), 608 (m), 566 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (br s, 1 H, indole NH), 7.88–7.83 [m, 2 H, N(C(=O)CC*H*CH)$_2$], 7.79–7.77 (m, 1 H, indole 4-H), 7.73–7.68 [m, 2 H, N(C(=O)CCHC*H*)$_2$], 7.32–7.27 (m, 1 H, indole 7-H), 7.16–7.10 (m, 2 H, indole 5-H, indole 6-H), 6.17 [dd, ^3J = 17.4, 10.6 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.22 [dd, ^3J = 10.4 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.19 [dd, ^3J = 3.5 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 3.93–3.89 (m, 2 H, CCH$_2$C*H*$_2$N), 3.20–3.15 (m, 2 H, CC*H*$_2$CH$_2$N), 1.62 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 [2 C, N(*C*(=O)CCHCH)$_2$], 145.6 [CH_2=*C*H(CH_3)$_2$C], 140.1 (indole C-2), 134.1 (indole C-7a), 133.8 [2 C, N(C(=O)CCH*C*H)$_2$], 132.3 [2 C, N(C(=O)*C*CHCH)$_2$], 129.6 (indole C-3a), 123.1 [2 C, N(C(=O)C*C*HCH)$_2$], 121.5 (indole C-6), 119.6 (indole C-5), 118.3 (indole C-4), 112.3 [*C*H$_2$=CH(CH_3)$_2$C], 110.4 (indole C-7), 107.1 (indole C-3), 38.9 [CNHC*C*(CH_3)$_2$CH], 38.4 (CNHCCCH$_2$*C*H$_2$N), 27.7 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 24.6 (CNHCC*C*H$_2$CH$_2$N).

MS (EI, 70 eV): *m*/*z* (%) = 358 ([M]$^+$, 100), 290 ([M – C_5H_9 + H]$^+$, 12), 289 ([M – C_5H_9]$^+$, 25), 210 (32).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{22}N_2O_2$ [M]$^+$: 358.1676; found: 358.1676.

UV ($CHCl_3$): λ_{max} (lg ε) = 283 (3.97), 242 nm (4.21).

2-[2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethanamine (16)

To a solution of N_b-phthalic-2-*tert*-prenyltryptamine **15** (1.0 g, 2.79 mmol, 1.0 equiv) in CH_2Cl_2–MeOH (1:1, 30 mL) was added NH_2NH_2·H_2O (0.38 mL, 7.82 mmol, 2.8 equiv) at r.t. The reaction mixture was stirred for 48 h and poured into H_2O (60 mL). After extraction with Et_2O (4 × 100 mL), the combined organic extracts were washed with aq 1 M HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of

the residual oil (silica gel, $CHCl_3$–MeOH, 6:1) afforded compound **16** (0.43 g, 1.61 mmol, 58%) as a colorless oil; R_f = 0.23 ($CHCl_3$–MeOH, 6:1).

IR (ATR): 3432 (w), 3140 (w), 3057 (w), 2965 (m), 2928 (m), 2871 (m), 1585 (m), 1460 (m), 1360 (w), 1340 (w), 1306 (m), 1228 (w), 1031 (w), 1009 (m), 905 (s, br), 734 cm^{-1} (s, br).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (br s, 1 H, indole NH), 7.55 (d, ^3J = 7.8 Hz, 1 H, indole 4-H), 7.28 (dt, ^4J = 0.9 Hz, ^3J = 7.8 Hz, 1 H, indole 7-H), 7.12 (dt, ^4J = 1.3 Hz, ^3J = 7.5 Hz, 1 H, indole 6-H), 7.07 (dt, ^4J = 1.2 Hz, ^3J = 7.4 Hz, 1 H, indole 5-H), 6.13 [dd, ^3J = 17.4, 10.6 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.17 [dd, ^3J = 9.4 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.14 [dd, ^3J = 2.5 Hz, ^2J = 1.0 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 3.02 (br s, 4 H, CC*H*$_2$C*H*$_2$NH_3^+Cl), 2.34 (br s, 3 H, CCH$_2$CH$_2$N*H*$_3^+$Cl), 1.54 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0 [CH_2=*C*H(CH_3)$_2$C], 139.7 (indole C-2), 134.1 (indole C-7a), 129.8 (indole C-3a), 121.4 (indole C-6), 119.2 (indole C-5), 118.3 (indole C-4), 112.0 [*C*H$_2$=CH(CH_3)$_2$C], 110.4 (indole C-7), 108.4 (indole C-3), 43.0 (2 C, CNHCC*C*H$_2$C*H*$_2$N), 39.0 [CNHC*C*(CH_3)$_2$CH], 27.8 [2 C, CH_2=CH(*C*H$_3$)$_2$C].

MS (EI, 70 eV): *m*/*z* (%) = 229 ([M + H]$^+$, 4), 228 ([M]$^+$, 23), 198 (100), 183 (56), 168 (41).

GC-HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}N_2$ [M]$^+$: 228.1621; found: 228.1630.

UV ($CHCl_3$): λ_{max} (lg ε) = 283 (3.83), 240 nm (3.92).

3a-(2-Methylbut-3-en-2-yl)-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indole (17)

To a solution of 2-*tert*-prenyltryptamine **16** (100 mg, 0.38 mmol, 1.0 equiv) in THF (15 mL) was added NBS (79 mg, 0.44 mmol, 1.16 equiv) at r.t. The reaction mixture was stirred at 0 °C for 35 min, before $CHCl_3$ (50 mL) was added. The organic layer was washed with aq 2 M NaOH (3 × 40 mL) and H_2O (3 × 40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residual green solid was purified by column chromatography over silica gel ($CHCl_3$–MeOH, 7:1 to 5:1) to afford compound **17** (47 mg, 0.21 mmol, 55%) as a green amorphous solid; R_f = 0.45 ($CHCl_3$–MeOH; 5:1); mp 160 °C.

IR (ATR): 3053 (w), 2968 (m), 2929 (m), 2874 (m), 2819 (m), 2738 (w), 1672 (s), 1638 (w), 1608 (m), 1455 (s), 1419 (m), 1380 (w), 1331 (m), 1233 (m), 1196 (m), 1153 (m), 1106 (m), 999 (m), 921 (s), 816 (m), 798 (w), 741 (s), 708 (s), 654 (m), 610 (m), 539 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (br s, 8-H), 7.17 (dt, ^4J = 1.3 Hz, ^3J = 7.7 Hz, 1 H, 6-H), 7.11 (dd, ^4J = 0.8 Hz, ^3J = 7.4 Hz, 1 H, 4-H), 6.89 (dd, ^4J = 1.1 Hz, ^3J = 8.3 Hz, 1 H, 5-H), 6.86 (dd, ^4J = 1.0 Hz, ^3J = 7.5 Hz, 1 H, 7-H), 6.03 [dd, ^3J = 17.1, 11.0 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.05 [s, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.01 [dd, ^3J = 8.0 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 3.93 (ddd, ^3J = 9.3, 5.8 Hz, ^2J = 12.4 Hz, 1 H, CNHC=NC*H*$_2$CH$_2$C), 3.82 (dd, ^3J = 9.0 Hz, ^2J = 12.4 Hz, 1 H, CNHC=NC*H*$_2$CH$_2$C), 2.43 (dd, ^3J = 5.2 Hz, ^2J = 13.0 Hz, 1 H, CNHC=NCH$_2$C*H*$_2$C), 2.13 (dt, ^3J = 6.4 Hz, ^2J = 16.7 Hz, 1 H, CNHC=NCH$_2$C*H*$_2$C), 1.03 [s, 3 H, CH_2=CH(C*H*$_3$)$_2$C], 0.95 [s, 3 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.1 (C-8a), 152.5 (C-7a), 143.6 [CH_2=*C*H(CH_3)$_2$C], 134.4 (C-3b), 128.3 (C-6), 124.7 (C-4), 120.4 (C-7), 113.2 [*C*H$_2$=CH(CH_3)$_2$C], 112.0 (C-5), 65.5 (C-3a), 57.5 (C-2), 43.4 [CNHC(=N)C*C*(CH_3)$_2$CH], 32.1 (C-3), 22.9 [CH_2=CH(*C*H$_3$)$_2$C], 21.9 [CH_2=CH(*C*H$_3$)$_2$C].

MS (EI, 70 eV): *m*/*z* (%) = 226 ([M]$^+$, 20), 157 ([M – C_5H_9]$^+$, 100), 156 (30), 130 (32).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}N_2$ [M]$^+$ 226.1465; found: 226.1464.

UV ($CHCl_3$): λ_{max} (lg ε) = 258 nm (3.73).

N-{2-[2-(2-Methylbut-3-en-2-yl)-1*H*-indol-3-yl]ethyl}formamide (18)

A mixture of Ac_2O (0.23 mL, 2.42 mmol, 2.5 equiv) and HCO_2H (0.1 mL, 2.42 mmol, 2.5 equiv) was stirred at 60 °C for 1 h. After cooling to r.t., a solution of 2-*tert*-prenyltryptamine **16** (221 mg, 0.97 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at r.t. for 2 h. Upon completion, the mixture was added to aq 12 M NaOH (14 mL) and ice (15 g). The alkaline mixture was diluted with CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with aq 2 M HCl (2 × 30 mL), H_2O (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford compound **18** (240 mg, 0.94 mmol, 97%) as an oil.

IR (ATR): 3299 (w, br), 3056 (w), 2968 (w), 2868 (w), 1660 (s, br), 1517 (w), 1460 (m), 1435 (m), 1383 (m), 1338 (w), 1304 (w), 1238 (m, br), 1173 (w), 1006 (w), 915 (m), 741 cm^{-1} (s, br).

NMR: Ratio of rotamers in $CDCl_3$ = 1:0.2.

^1H NMR (400 MHz, $CDCl_3$): δ (major) = 8.12 (s, 1 H, CHO), 8.02 (br s, 1 H, indole NH), 7.55 (dt, ^4J = 0.5 Hz, ^3J = 7.7 Hz, 1 H, indole 4-H), 7.30 (dt, ^4J = 0.9 Hz ^3J = 8.0 Hz, 1 H, indole 7-H), 7.14 (td, ^4J = 1.3 Hz ^3J = 7.4 Hz, 1 H, indole 6-H), 7.09 (td, ^4J = 1.2 Hz ^3J = 7.4 Hz, 1 H, indole 5-H), 6.12 [dd, ^3J = 17.7, 10.3 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.67 (br s, 1 H, CH$_2$N*H*CHO), 5.17 [dd, ^3J = 6.2 Hz, ^2J = 0.9 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_Z$], 5.14 [d, ^2J = 1.2 Hz, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 3.58 (q, ^3J = 13.8, 6.9 Hz, 2 H, CCH$_2$C*H*$_2$NHCHO), 3.08 (t, ^3J = 7.3 Hz, 2 H, CC*H*$_2$CH$_2$NHCHO), 1.54 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) = 161.2 (CHO), 145.8 [CH_2=*C*H(CH_3)$_2$C], 140.2 (indole C-2), 134.2 (indole C-7a), 129.6 (indole C-3a), 121.5 (indole C-6), 119.6 (indole C-5), 118.1 (indole C-4), 112.1 [*C*H$_2$=CH(CH_3)$_2$C], 110.5 (indole C-7), 107.4 (indole C-3), 39.0 [NHC*C*(CH_3)$_2$CH], 38.8 (CCH$_2$*C*H$_2$NHCHO), 27.8 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 24.9 (C*C*H$_2$CH$_2$NHCHO).

^1H NMR (400 MHz, $CDCl_3$): δ (minor) = 7.97 (s, 1 H, CHO), 7.94 (br s, 1 H, indole NH), 7.45 (dt, ^4J = 0.6 Hz, ^3J = 7.8 Hz, 1 H, indole 4-H), 7.31 (dt, ^4J = 0.9 Hz ^3J = 7.9 Hz, 1 H, indole 7-H), 7.15 (td, ^4J = 1.4 Hz ^3J = 6.7 Hz, 1 H, indole 6-H), 7.15–7.06 (m, 1 H, indole 5-H), 6.12 [dd, ^3J = 17.7, 10.3 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.67 (br s, 1 H, CH$_2$N*H*CHO), 5.18 [dd, ^3J = 6.7 Hz, ^2J = 1.2 Hz, 1 H, C*H*$_2$ =CH(CH_3)$_2$C-H$_Z$], 5.14 [s, 1 H, C*H*$_2$=CH(CH_3)$_2$C-H$_E$], 3.54–3.46 (m, 2 H, CCH$_2$C*H*$_2$NHCHO), 3.13–3.04 (m, 2 H, CC*H*$_2$CH$_2$NHCHO), 1.53 [s, 6 H, CH_2=CH(C*H*$_3$)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ (minor) = 164.3 (CHO), 145.9 [CH_2=*C*H(CH_3)$_2$C], 140.2 (indole C-2), 134.2 (indole C-7a), 129.6 (indole C-3a), 121.7 (indole C-6), 119.4 (indole C-5), 117.8 (indole C-4), 112.0 [*C*H$_2$=CH(CH_3)$_2$C], 110.7 (indole C-7), 106.6 (indole C-3), 42.1 (CCH$_2$*C*H$_2$NHCHO), 39.0 [NHC*C*(CH_3)$_2$CH], 28.1 [2 C, CH_2=CH(*C*H$_3$)$_2$C], 25.3 (C*C*H$_2$CH$_2$NHCHO).

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M]$^+$, 27), 198 ([M – C_2H_4NO]$^+$, 100), 184 ([M – C_3H_6NO]$^+$, 9), 168 (48).

GC-HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}N_2$ [M]$^+$: 256.1576; found: 256.1572.

UV ($CHCl_3$): λ_{max} (lg ε) = 283 (3.79), 240 (3.88), 232 nm (3.69).

rac-Dihydroflustramine C (25)

At r.t., DIBAL-H (20% in toluene, 0.48 mL, 0.57 mmol, 1.8 equiv) was added dropwise to a solution of *rac*-flustramine C (**1**; 100 mg, 0.31 mmol, 1.0 equiv) in THF (10 mL) under Ar. The reaction mixture was stirred at r.t. for 26 h and then added dropwise to ice water (250 mL). The mixture was diluted with Et_2O (75 mL) and made strongly alkaline with aq 12 M NaOH (35 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), washed with H_2O (3 × 50

mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford *rac*-dihydroflustramine C (**25**; 94 mg, 0.293 mmol, 93%) as a yellow oil; R_f = 0.2 (hexanes–EtOAc, 1:1).

IR (ATR): 3413 (w, br), 3260 (w, br), 3081 (w), 3033 (w), 2965 (m), 2935 (m), 2870 (w), 2843 (w), 2790 (w), 1595 (s), 1481 (s), 1446 (s), 1414 (m), 1380 (w), 1365 (m), 1349 (m), 1310 (m), 1249 (m, br), 1155 (m), 1120 (m), 1097 (w), 1072 (m), 1048 (m), 1004 (s), 942 (w), 910 (s), 886 (m), 834 (m), 789 (s), 687 (m), 605 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, ^3J = 7.0 Hz, 1 H, 4-H), 6.77 (dd, ^4J = 1.7 Hz, ^3J = 8.0 Hz, 1 H, 5-H), 6.67 (d, ^4J = 1.7 Hz, 1 H, 7-H), 5.96 [dd, ^3J = 17.4 Hz, 10.8 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.07 [dd, ^3J = 10.8 Hz, ^2J = 1.2 Hz, 1 H, CH_2=CH(CH_3)$_2$C-H$_Z$], 5.01 [dd, ^3J = 17.4 Hz, ^2J = 1.2 Hz, 1 H, CH_2=CH(CH_3)$_2$C-H$_E$], 4.39 (s, 1 H, 8a-H), 4.26 (br s, 1 H, 8-H), 2.59 (ddd, ^3J = 6.9, 4.2, 2.1 Hz, ^2J = 11.7 Hz, 1 H, CH_2CH_2NCH$_3$), 2.52 (ddd, ^3J = 6.1, 4.9, 3.7 Hz, ^2J = 1.2 Hz, 1 H, CH_2CH_2NCH$_3$), 2.37 (s, 3 H, NCH$_3$), 2.27 (ddd, ^3J = 9.7, 7.1, 2.0 Hz, ^2J = 12.2 Hz, 1 H, CH_2CH$_2$NCH$_3$), 1.79 (ddd, ^3J = 5.5, 5.0 Hz, ^2J = 12.0 Hz, 1 H, CH_2CH$_2$NCH$_3$), 1.03 [s, 3 H, CH_2=CH(CH_3)$_2$C], 0.99 [s, 3 H, CH_2=CH(CH_3)$_2$C].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.0 (C-7a), 144.6 (CH_2=*C*H(CH_3)$_2$C), 132.6 (C-3b), 126.2 (C-4), 121.2 (C-6), 120.6 (C-5), 113.1 [*C*H$_2$=CH(CH_3)$_2$C], 111.5 (C-7), 84.4 (C-8a), 63.9 (C-3a), 53.0 (C-2), 41.2 [HNCHC*C*(CH_3)$_2$], 36.8 (NCH$_3$), 34.7 (C-3), 23.1 [CH_2=CH(*C*H$_3$)$_2$C], 22.3 [CH_2=CH(*C*H$_3$)$_2$C].

MS (EI, 70 eV): *m*/*z* (%) = 320 ([M]$^+$, 22), 249 ([M – C_5H_9]$^+$, 100), 207 (32), 172 (43).

GC-HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}{}^{79}BrN_2$ [M]$^+$: 320.0883; found: 320.0883; *m*/*z* calcd for $C_{16}H_{21}{}^{81}BrN_2$ [M]$^+$: 322.0862; found: 322.0864.

UV (MeOH): λ_{max} (lg ε) = 308 (3.58), 251 (3.75), 228 nm (3.91).

rac-Debromodihydroflustramine C (26)

At r.t., DIBAL-H (1.0 M in toluene, 0.6 mL, 0.61 mmol, 1.85 equiv) was added dropwise to a solution of *rac*-debromoflustramine C (**7**; 80 mg, 0.33 mmol, 1.0 equiv) in THF (5 mL) under argon. The reaction mixture was stirred at r.t. for 24 h and then added dropwise to ice water (60 mL). Et_2O (30 mL) was added, followed by aq 12 M NaOH (20 mL). After extraction with Et_2O (3 × 20 mL), the combined ethereal layers were washed with H_2O (3 × 30 mL) and brine (20 mL), and dried (Na_2SO_4). Concentration in vacuo and column chromatography (silica gel, $CHCl_3$–MeOH, 5:1) afforded *rac*-debromodihydroflustramine C (**26**; 58 mg, 0.24 mmol, 73%) as a yellow oil; R_f = 0.2 ($CHCl_3$–MeOH, 5:1).

IR (ATR): 3259 (w, br), 3082 (w), 2964 (m), 2932 (m), 2872 (w), 2790 (w), 2659 (w), 2469 (w), 1669 (w), 1604 (m), 1483 (m), 1467 (s), 1414 (w), 1381 (w), 1365 (w), 1350 (w), 1316 (w), 1257 (w), 1153 (m), 1077 (w), 1004 (m), 913 (m), 740 (s), 689 cm^{-1} (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (ddd, ^4J = 0.4, 1.2 Hz, ^3J = 7.5 Hz, 1 H, 4-H), 7.08 (dt, ^4J = 1.2 Hz, ^3J = 7.6 Hz, 1 H, 6-H), 6.74 (dt, ^4J = 1.0 Hz, ^3J = 7.5 Hz, 1 H, 5-H), 6.65 (d, ^3J = 7.8 Hz, 1 H, 7-H), 5.99 [dd, ^3J = 17.4, 10.8 Hz, 1 H, CH_2=C*H*(CH_3)$_2$C], 5.10 [dd, ^3J = 1.3 Hz, ^2J = 10.8 Hz, 1 H, CH_2=CH(CH_3)$_2$C-H$_Z$], 5.03 [dd, ^3J = 1.3 Hz, ^2J = 17.3 Hz, 1 H, CH_2=CH(CH_3)$_2$C-H$_E$], 4.82 (br s, 1 H, 8a-H), 2.993–2.92 [m, 1 H, (CH_3)NCH_2CH$_2$C], 2.59–2.51 [m, 1 H, (CH_3)NCH_2CH$_2$C], 2.54 (s, 3 H, NCH$_3$), 2.45 [ddd, ^3J = 9.5, 6.5 Hz, ^2J = 12.2, 1 H, (CH_3)NCH$_2$CH_2C], 1.98 (ddd, ^3J = 5.7, 3.2 Hz, ^2J = 12.4 Hz, 1 H, CH_3NCH$_2$CH_2C), 1.08 [s, 3 H, CH_2=CH(CH_3)$_2$C], 1.03 [s, 3 H, CH_2=CH(CH_3)$_2$C].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0 (C-7a), 144.3 [CH_2=*C*H(CH_3)$_2$C], 132.2 (C-3b), 128.3 (C-6), 125.0 (C-4), 118.9 (C-5), 113.7 [*C*H$_2$=CH(CH_3)$_2$C], 109.4 (C-7), 88.4 (C-8a), 64.5 (C-3a), 53.2 (C-2), 41.3 [NHCHC*C*(CH_3)$_2$CH=CH$_2$], 36.3 (NCH$_3$), 33.9 (C-3), 23.2 [CH_2=CH(*C*H$_3$)$_2$C], 22.5 [CH_2=CH(*C*H$_3$)$_2$C].

MS (EI, 70 eV): *m*/*z* (%) = 242 ([M]$^+$, 22), 174 ([M – C_5H_9 + H]$^+$, 24), 173 ([M – C_5H_9]$^+$, 100), 130 (42).

GC-HRMS (EI): *m*/*z* calcd for $C_{16}H_{22}N_2$ [M]$^+$: 242.1778; found: 242.1762.

UV ($CHCl_3$): λ_{max} (lg ε) = 294 (3.37), 243 nm (3.75).

X-ray Structure Determination

Intensity data were recorded on an Oxford Diffraction Xcalibur E diffractometer at –173 °C using monochromated Mo-*K*α radiation (λ = 0.71073 Å) (Table 1). Absorption corrections were performed on the basis of multiscans. Structures were refined anisotropically on F^2 using SHELXL-97.[16] Hydrogens of NH groups were refined freely, other H using a riding model or rigid methyl groups. Solvent molecules were well-ordered.

Table 1 Details of X-ray Structure Analyses of Compounds **9** and **12**[17]

Parameters	**9**·CH_2Cl_2	**12**·$CDCl_3$
Formula	$C_{18}H_{25}BrCl_2N_2$	$C_{18}H_{25}DBrCl_3N_2$
M_r	420.21	457.68
Space group	*P*(-1)	$P2_1/n$
a (Å)	7.7569(3)	9.2879(3)
b (Å)	10.4033(4)	22.6454(6)
c (Å)	12.9292(6)	10.3652(3)
α (°)	73.847(4)	90
β (°)	78.274(4)	105.571(4)
γ (°)	72.065(4)	90
V (Å^3)	945.43	2100.1
Z	2	4
D_x (g/cm^3)	1.476	1.444
μ (/mm)	2.5	2.3
F(000)	432	936
Habit	colorless prism	colorless lath
Size	0.3 × 0.2 × 0.15	0.4 × 0.2 × 0.1
2θ (max) (°)	60	56.6
No. of refl.	58212	68893
Unique refl.	5457	5197
R(int)	0.030	0.057
No. of parameters	212	229
*wR*2 (all data)	0.052	0.063
*R*1 [$I > 4\sigma(I)$]	0.021	0.028
S	0.99	0.94
Max. Δρ (e/Å^3)	0.68	0.74

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by generous donation of solvents (BASF AG, Honeywell) and chromatography materials (Merck KGaA).

References

(1) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440.
(2) (a) Lysek, N.; Rachor, E.; Lindel, T. *Z. Naturforsch., C* **2002**, *57*, 1056. (b) Peters, L.; König, G. M.; Terlau, H.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1633. (c) Peters, L.; Wright, A. D.; Krick, A.; König, G. M. *J. Chem. Ecol.* **2004**, *30*, 1165.
(3) Lindel, T.; Bräuchle, L.; Golz, G.; Böhrer, P. *Org. Lett.* **2007**, *8*, 283.
(4) Grubbs, A. W.; Artman, G. D. III; Tsukamoto, S.; Williams, R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2257.
(5) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63.
(6) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9089.
(7) Transition metal-catalyzed 3-*tert*-prenylation of indole: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (b) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207. (c) Gruber, S.; Zaitsev, A. B.; Wörle, M.; Pregosin, P. S. *Organometallics* **2008**, *27*, 3796..
(8) (a) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964.
(9) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711.
(10) Antelo, J. M.; Arce, F.; Crugeira, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2275.
(11) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576.
(12) Hino, T.; Endo, M.; Tonozuka, M.; Hashimoto, Y.; Nakagawa, M. *Chem. Pharm. Bull.* **1977**, *25*, 2350.
(13) Wright, J. L. C. *J. Nat. Prod.* **1984**, *47*, 893.
(14) Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9.
(15) (a) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9. (b) It proved to be beneficial if 1,1-dimethylallene and 9-BBN-H were allowed to react for 18 h at r.t. before use.
(16) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.
(17) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications No. CCDC 773395 (**9**), 773396 (**12**). Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.