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A stereoselective synthetic approach to (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′,3′-epoxypropyl)-3-hydroxytryptophan, a component of cyclomarin A

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Abstract—A stereoselective synthetic approach to (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′,3′-epoxypropyl)-3-hydroxytryptophan an amino acid contained in cyclomarin A was accomplished. The synthesis is based on a diastereoselective addition of an indole Grignard into a chiral serine aldehyde equivalent.

1. Introduction

Cyclomarin A is a novel cyclic peptide isolated from a marine actinomycete collected in a sediment sample from Mission Bay, California[1] (Fig. 1). Cyclomarin A has demonstrated potent biological activity, having a mean IC_{50} of 2.6 μM against a panel of human cancer cells. More impressive was its anti-inflammatory activity both in vitro and in vivo, exhibiting a 92% inhibition of edema in the phorbol ester induced mouse ear edema assay at the standard testing dose. The combination of biological activity and complex molecular architecture has attracted the interest of several synthetic groups, culminating in the synthesis of cyclomarin C,[2] a close congeners of cyclomarin A and two independent syntheses of (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′-propenyl)-3-hydroxytryptophan.[3,4] We herein report a synthesis of a fully protected analogue of (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′,3′-epoxypropyl)-3-hydroxytryptophan **1** based on Lajoie's serine aldehyde.

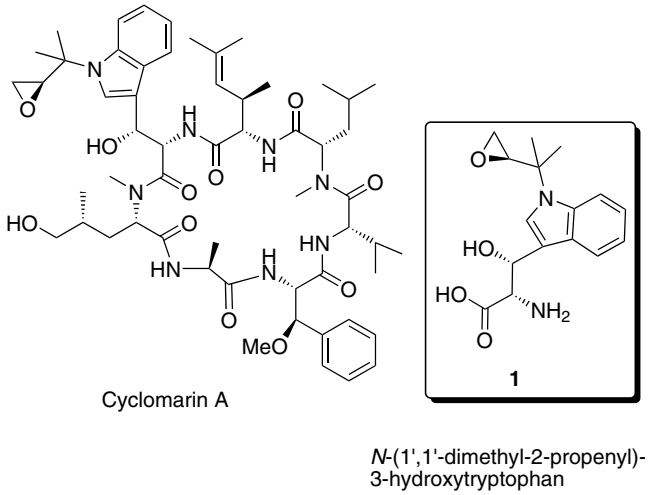

Figure 1. Cyclomarin A and (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2,3-epoxypropyl)-3 hydroxytryptophan **1**.

2. Results and discussion

Nucleophilic additions into aldehydes derived from serine have been a powerful method for the construction of non-coded amino acids. Garner's aldehyde has been one of the most popular variants of this methodology.[5] We examined the possibility of using Garner's aldehyde, which we have used extensively in the past, but we were also intrigued by a similar serine aldehyde developed by Lajoie.[6,7] Lajoie's chiral serine aldehyde seemed to solve many of the problems associated with the limited stereocontrol during nucleophilic additions to Garner's aldehyde. The high stereoselectivity of the addition also complements the use of the Sharpless amino hydroxylation reaction used by Sugiyama et al. in their synthesis of the β-hydroxytryptophan moiety, because this reaction can be equally complicated because of a mixture

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of regioisomers resulting in modest yields. Retrosynthetically, we thought that a properly protected β-hydroxytryptophan moiety could be derived from an *ortho* ester intermediate that would come from the addition of an indole derived Grignard with Lajoie's serine aldehyde (Fig. 2).

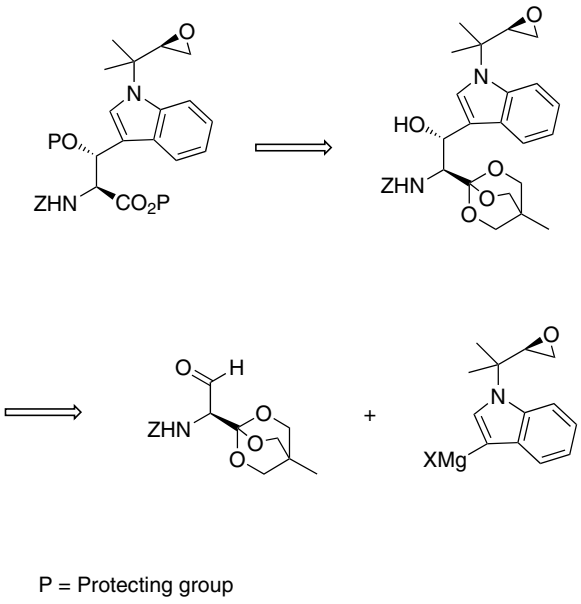
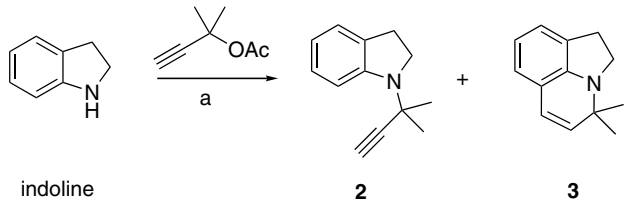


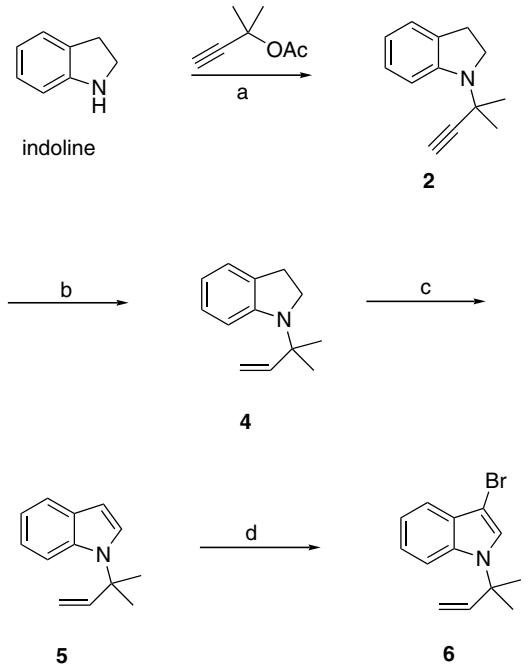
Figure 2. Retrosynthetic analysis of **1**.

The synthesis of the indole Grignard precursor is based on the work by Sugiyama who has shown that indoline can be transformed into a variety of indole Grignard precursors.[8] Construction of the indole Grignard precursor began from indoline, using a copper-catalyzed reverse prenylation to provide alkyne **2** (Scheme 2). It was found that this reaction must be monitored closely to prevent the formation of a side product of nearly identical R_f from contaminating alkyne **2**. Prolonged reflux of this reaction allowed for identification of this intermediate **3** (Scheme 1). This undesired side reaction made this chemistry unfeasible for the total synthesis and chromatographic separation of compounds **2** and **3**. To better understand this side reaction, we decided to explore the formation of **3**. Our first goal was to determine if **3** was formed directly from the indoline and the alkyne acetate or whether the reaction occurred after the formation of **2**. Exposure of **2** to refluxing THF showed the slow formation of **3**. It was found that the reaction could be driven to completion by using a combination of higher temperature and microwave irradiation. To prevent the formation of **3**, the reaction was left to reflux for 3.5 h to give alkyne **2** in good yield.

Selective reduction of the triple bond provided alkene **4**. Oxidation of the indoline ring was accomplished with MnO_2 to give indole **5**. The reaction worked well but took 3 days for completion. In an effort to reduce the reaction time, we investigated the use of DDQ as an oxidant, but found it to be inferior to MnO_2 giving lower yields and more impurities. Finally, bromination occurred smoothly in the presence of NBS to give indole



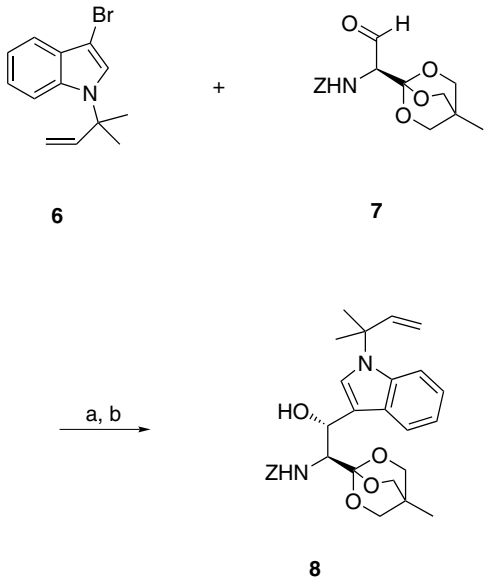
Scheme 1. Reagents and conditions: (a) CuCl, TEA.



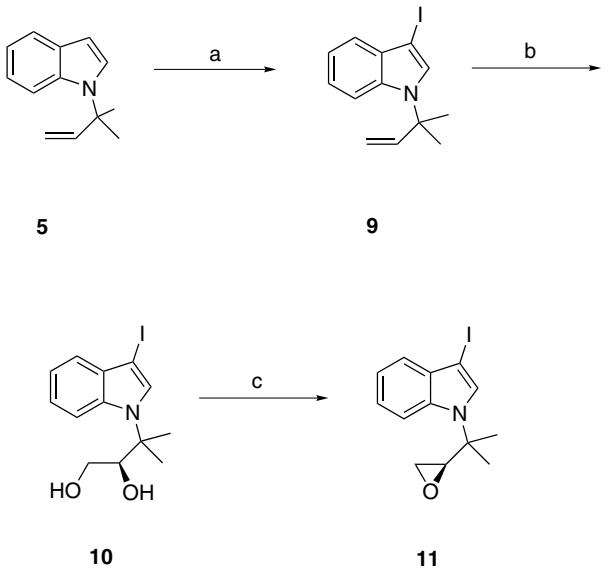
Scheme 2. Reagents and conditions: (a) CuCl, NEt_3, 84%; (b) Lindlar Cat., H_2, 86%; (c) MnO_2, 84%; (d) NBS, 70%.

6. At this point in the synthesis, we opted to forego the formation of the epoxide, and evaluate the Grignard addition of bromoindole **6** into the serine aldehyde. Classical Grignard conditions of Mg, I_2, and refluxing diethyl ether overnight consumed most of the magnesium. The reaction was cooled to room temperature and a solution of serine aldehyde **7** then added. After work-up and chromatography, a moderate yield of the desired β-hydroxy intermediate **8** was isolated (Scheme 3).

While the yield was lower than previous Grignard additions to serine aldehyde **7**, this reaction did show that 3-bromoindole could serve as a suitable Grignard precursor. Intermediate **8** may prove to be a valuable intermediate at a later point because complete deprotection would yield *N*-(1′,1′-dimethyl-2′-propenyl)-β-hydroxytryptophan, which is one of the amino acids present in cyclomarin C. Next, we examined the formation of the terminal epoxide. The number of existing methods to construct chiral terminal epoxides are limited. We considered using a direct epoxidation method such as Shi's chiral ketone catalyzed asymmetric epoxidation, however substrates similar to our mono substituted olefin gave lower than desired ees. Therefore, we chose an asymmetric dihydroxylation (AD) to install



Scheme 3. Reagents and conditions: (a) Mg turnings, I_2; (b) CH_2Cl_2, 37% yield, 85% de.



Scheme 4. Reagents and conditions: (a) NIS, 87%; (b) $(DHQD)_2PYR$, $K_2[OsO_2(OH)_4]$, $K_3Fe(CN)_6$ 80% yield, 91% ee; (c) TsCl, NEt_3, $Me_3N{\cdot}HCl$, 74% over two steps.

the terminal epoxide as it appeared to afford the highest ees. According to Sugiyama et al., who investigated the Sharpless asymmetric dihydroxylation of similar *N*-(1′,1′-dimethyl-2′,3′-epoxypropyl)indoles, the use of Sharpless's second generation $(DHQD)_2PYR$ ligand gave the highest ees of the desired diol. We, therefore, examined the Sharpless's AD reaction on a number of the intermediates **4**, **5**, and **6** and found that the reaction proceeded most efficiently on indole **9**.

Previously we found that the formation of the indole Grignard from 3-bromoindole **6** was sluggish and required prolonged refluxing for its formation. We felt that such conditions might imperil the terminal epoxide and decided to use instead a tandem lithium–halogen exchange followed by transmetalation to magnesium. Exposure of **6** to *n*-BuLi at −78 °C proceeded slowly and even after 6 h not all of the starting materials had been consumed. It is well known that 3-lithioindole derivatives can migrate to the 2-position at higher temperatures and we were therefore not willing to increase the temperature beyond −78 °C. In an effort to facilitate the halogen–lithium exchange, we decided to examine a 3-iodoindole because iodine is more reactive toward lithium–halogen exchange. Starting with indole **5**, iodination occurred smoothly with NIS to afford **9**. Asymmetric dihydroxylation with Sharpless's second generation ligand $(DHQD)_2PYR$ gave diol **10** in high yield and 91% ee (Scheme 4). Epoxide formation was accomplished in a two-step, one-pot procedure. Tosylation of the primary alcohol of diol **10** with TsCl, triethylamine, and catalytic trimethylamine hydrochloride[9] afforded a quantitative conversion of terminal tosylate, after which the addition of K_2CO_3 gave terminal epoxide **11** in good yield.

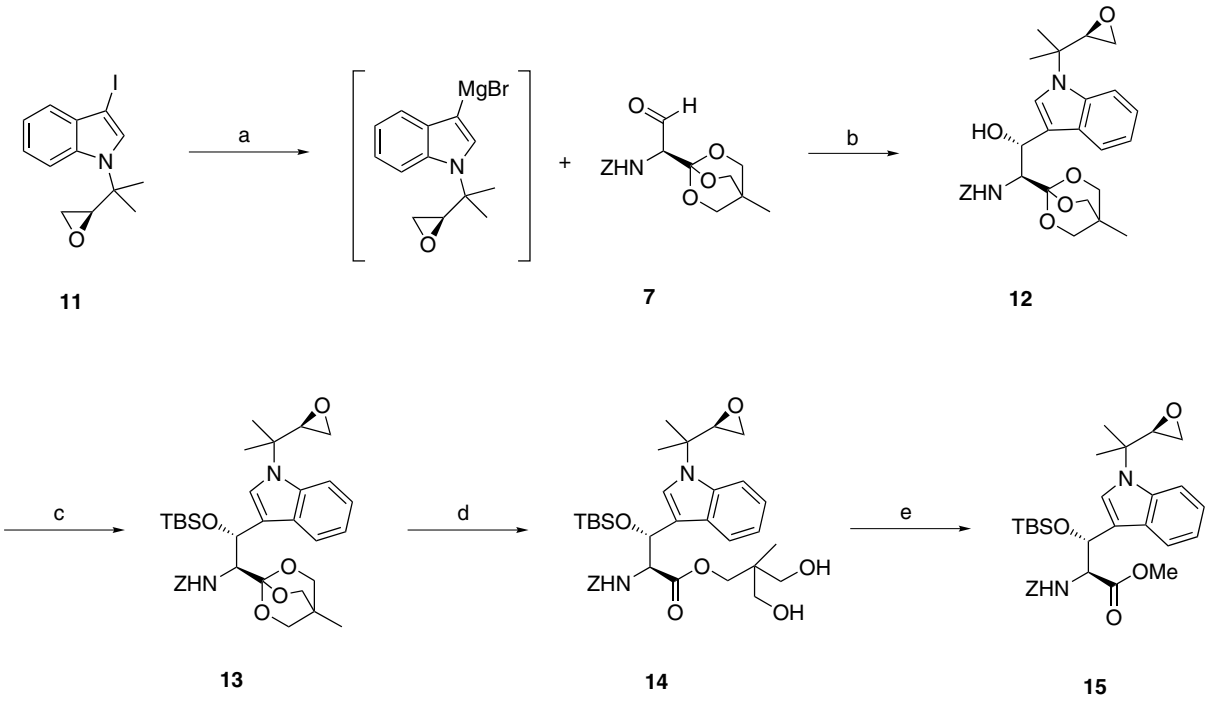
Exposure of indole **11** to *n*-BuLi, followed by $MgBr_2$ and the addition of serine aldehyde **7**, gave a low yield of the desired β-hydroxy intermediate **12** (Scheme 5). The lower than anticipated yield was disappointing but with further optimization the yield can probably be improved. The hydroxyl group of **12** was protected as a TBS ether to give **13**, followed by treatment with aqueous acetic acid to give a good yield of diol-ester **14**. Basic hydrolysis of the ester with LiOH provided a crude acid that was treated with $TMSCHN_2$ to give the desired methyl ester **15**. Our ability to cleave the diol-ester to give the crude acid, should also allow for direct elaboration with an amino acid for the construction of cyclomarin A.

3. Conclusion

A stereoselective synthesis of a fully protected intermediate toward the synthesis of (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′,3′-epoxypropyl)-3-hydroxytryptophan **1** has been accomplished. Our ability to add highly functionalized Grignard reagents in a stereoselective fashion to Lajoie's chiral serine aldehyde is a significant extension of this synthetically useful method for the synthesis of β-hydroxy amino acids.

4. Experimental

Reactions requiring air-sensitive manipulations were conducted under an argon atmosphere. Methylene chloride was distilled from calcium hydride, while tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. Analytical TLC was performed on 0.25 mm E. silica gel 60 F_{254} plates. Silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a 500 MHz spectrometer and calibrated by using residual undeuterated solvent or TMS as the internal reference.



Scheme 5. Reagents and conditions: (a) (1) *n*-BuLi, (2) $MgBr_2$; (b) CH_2Cl_2, 24% yield, 88% de; (c) TBSOTf, proton sponge®, 64%; (d) HOAc, dioxane, water, 75%; (e) (1) LiOH, (2) $TMSCHN_2$ 38% yield two steps.

Chemical shifts (δ) were measured in parts per million, while coupling constants (J values) are given in Hertz (Hz). Infrared spectra (IR) were recorded on an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI). Optical rotations were recorded on a polarimeter at the sodium D line. Melting points were determined in an open capillary tube and were uncorrected.

4.1. 1-(2-Methylbut-3-yn-2-yl)indoline 2

Indoline (30 mL, 0.27 mol), 2-methyl-3-butyn-2-ol (54 mL, 0.40 mol), CuCl (1.33 g, 13.4 mmol), and triethylamine (38 mL, 0.27 mol) were dissolved in THF (500 mL). The flask was fitted with a reflux condenser and allowed to reflux for 3.5 h until judged complete by TLC. The solvent was reduced in vacuo and the residue purified by flash silica gel chromatography, eluting with 1–10% EtOAc–Hex to give an orange oil (41.8 g, 84%): TLC (5% EtOAc–hexanes) $R_f = 0.40$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (d, $J = 8.0$, 1H), 7.09–7.05 (m, 2H), 6.71 (t, $J = 7.3$, 1H), 3.39 (t, $J = 8.1$, 2H), 2.91 (t, $J = 8.1$, 2H), 2.38 (s, 1H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 131.6, 126.6, 124.3, 118.3, 111.6, 87.4, 70.7, 51.00, 49.4, 28.1, 27.1; IR (thin film) 3285 m, 2985 m, 2932 w, 2834 w, 1598 s, 1480 s, 1454 m, 1382 w, 1355 w, 1330 w, 1303 w, 1258 s, 1225 s, 1199 s, 1166 m, 1062 w, 1029 w, 748 s; HRMS (CI): m/z calcd for $C_{13}H_{15}N$ 185.1205, found 185.1204.

4.2. 4,4-Dimethyl-2,4-dihydro-1*H*-pyrrolo[3,2,1]quinoline 3

Indoline (1.6 mL, 14.3 mmol), 2-methyl-3-butyn-2-ol (1.9 mL, 0.40 mmol), CuCl (5.0 mg), and triethylamine (2.0 mL, 14.3 mmol) were combined in a sealed tube. The reaction was heated to 160 °C for 30 min in a CEM mono-mode microwave reactor. The residue was purified by flash silica gel chromatography, eluting with 2% EtOAc–Hex to give a yellow oil (1.10 g, 42%): TLC (5% EtOAc–hexanes) $R_f = 0.32$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (d, $J = 7.3$, 1H), 6.72 (d, $J = 7.4$, 1H), 6.49 (t, $J = 7.4$, 1H), 6.26 (d, $J = 9.6$, 1H), 5.35 (d, $J = 9.6$, 1H), 3.53 (t, $J = 8.4$, 2H), 2.99 (t, $J = 8.4$, 2H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.30, 131.93, 126.4, 123.9, 122.9, 122.2, 117.0, 116.9, 55.4, 45.9, 28.1, 16.2; IR (thin film) 3049 m, 3025 m, 2963 s, 2928 s, 2862 m, 1632 s, 1607 m, 1485 s, 1437 m, 1382 m, 1281 s, 1234 s, 1138 m, 763 m, 744 s, 723 s; HRMS (CI): m/z calcd for $C_{13}H_{15}N$ 185.1205, found 185.1204.

4.3. 1-(2-Methylbut-3-en-2-yl)indoline 4

Indoline **2** (1.00 g, 5.40 mmol), Lindlar's catalyst (20.0 mg), and quinoline (2.4 mg, 0.019 mmol) were dissolved in MeOH (15 mL) in a Parr hydrogenation flask. The reaction mixture was allowed to shake under a H_2 atmosphere (45 psi) at room temperature for 30 min and judged to be complete by TLC. The reaction mixture was diluted with EtOAc and filtered through Celite. The solvent was removed in vacuo, and the residue was purified by flash silica gel chromatography, eluting with 2% EtOAc–hexanes to yield a yellow-orange oil (866 mg, 86%): TLC (5% EtOAc–hexanes) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (d, $J = 7.0$, 1H), 6.94 (dt, $J = 0.6$, $J = 8.0$, 1H), 6.78 (d, $J = 7.9$, 1H), 6.62 (dt, $J = 0.6$, $J = 7.4$, 1H), 6.16–6.10 (m, 1H), 5.22 (dd, $J = 0.9$, $J = 17.6$, 1H), 5.13 (dd, $J = 0.8$, $J = 10.7$, 1H), 3.43 (t, $J = 8.3$, 2H), 2.91 (t, $J = 8.3$,

2H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.7, 147.0, 131.4, 126.4, 126.14, 117.2, 112.1, 111.1, 57.3, 49.0, 28.1, 24.1; IR (thin film) 2975 s, 2842 m, 1605 s, 1485 s, 1460 s, 1412 w, 1382 m, 1352 m, 1328 m, 1304 w, 1255 s, 1195 s, 1171 m, 1026 m, 990 m, 917 m, 742 s; HRMS (CI): m/z calcd for $C_{13}H_{17}N_1$ 187.1361, found 187.1357.

4.4. 1-(2-Methylbut-3-en-2-yl)-1*H*-indole 5

Indoline **4** (30.75 g, 0.16 mol) and MnO_2 (71.38 g, 0.82 mmol) were combined in toluene (500 mL). The flask was fitted with a reflux condenser and the mixture was allowed to reflux for 3 days. The reaction was diluted with EtOAc and filtered through Celite. The solvent was reduced in vacuo, and the residue purified by flash silica gel chromatography, eluting with 2.5% EtOAc–hexanes to yield an orange oil (25.5 g, 84%): TLC (1% EtOAc–hexanes) $R_f = 0.21$; ^{1}H ($CDCl_3$, 500 MHz) δ 7.63–7.61 (m, 1H), 7.54–7.21 (m, 1H), 7.31 (d, $J = 3.3$, 1H), 7.13–7.06 (m, 2H), 6.49–6.48 (m, 1H), 6.17 (dd, $J = 10.7$, $J = 6.7$, 1H), 5.23–5.15 (m, 2H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.2, 135.3, 130.1, 125.0, 120.9, 120.6, 119.1, 113.7, 113.4, 100.6, 59.0, 27.9; IR (thin film) 2976 w, 1504 w, 1445 s, 1314 m, 1229 m, 1203 m, 915 m, 739 s; HRMS (CI): m/z calcd for $C_{13}H_{15}N$ 185.1204, found 185.1198.

4.5. 3-Bromo-1-(2-methylbut-3-en-2-yl)-1*H*-indole 6

Indole **5** (290 mg, 1.57 mmol) was dissolved in DMF (10 mL), and the solution cooled to 0 °C. NBS (278 mg, 1.57 mmol) was added and the reaction shielded from light and allowed to stir for 3 h at 0 °C. The reaction was judged to be complete by TLC and quenched with satd $NaHCO_3$ (10 mL), diluted with water (20 mL), and the aqueous layer extracted twice with Et_2O. The organic layers were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 2.5% EtOAc–Hex to give a yellow oil (289 mg, 70% yield): TLC (1% EtOAc–Hex), $R_f = 0.21$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57–7.55 (m, 1H), 7.52–7.50 (m, 1H), 7.31 (s, 1H), 7.18–7.15 (m, 2H), 6.16–6.11 (m, 1H), 5.25–5.16 (m, 2H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.6, 134.8, 128.6, 124.2, 121.8, 119.9, 119.3, 113.9, 89.4, 59.7, 27.9; IR (thin film) 3049 w, 2981 m, 2931 w, 1454 s, 1366 m, 1310 s, 1229 s, 1179 s, 924 m, 737 s; HRMS (EI): m/z calcd for $C_{13}H_{14}BrN$ 263.0310, found 263.0312.

4.6. Benzyl-(1*S*,2*R*)-2-hydroxy-1-(4″-methyl-2″,6″,7″-trioxabicyclo[2.2.2]octan-1″-yl)-2-[1-(2′-methylbut-3′-en-2′-yl)-1*H*-indol-3-yl]ethylcarbamate 8

Bromoindole **6** (1.00 g, 3.79 mmol) was dissolved in anhydrous THF (10 mL), magnesium turnings (100 mg, 4.17 mmol) then added to the solution, and the reaction refluxed under argon overnight. The next day, the magnesium turnings had been consumed and the reaction was cooled to room temperature, diluted with Et_2O (5 mL), and then cooled to 0 °C. Serine aldehyde **7** (385 mg, 1.20 mmol) dissolved in CH_2Cl_2 (10 mL) was added at 0 °C and the reaction mixture was allowed to stir for 10 min. The reaction was quenched with 5% aqueous NH_4Cl and diluted with Et_2O (50 mL). The organic layer was separated and washed with 5% aqueous NH_4Cl, and brine. The solution was dried over $MgSO_4$ and the solvent reduced in vacuo. The residue was redissolved in EtOAc (10 mL), and EtOH (10 mL) and $NaBH_4$ then added to reduce any remaining aldehyde. The reaction was stirred for 30 min, then quenched with 5% aqueous NH_4Cl and diluted with Et_2O (50 mL). The organic layer was washed with 5% aqueous NH_4Cl, brine, dried over $MgSO_4$, and reduced in vacuo. An 85% de was calculated from integrating the α proton of the crude product. The residue was purified by flash silica gel chromatography, eluting with 50% EtOAc–Hex to give a yellow oil (225 mg, 37% yield): $[\alpha]_D^{20} = -27.0$ (c 0.9, $CHCl_3$); TLC (50% EtOAc–Hex), $R_f = 0.28$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, $J = 6.5$, 1H), 7.43 (d, $J = 10.8$, 1H), 7.35–7.27 (m, 6H), 7.08–7.00 (m, 2H), 6.06 (dd, $J = 10.7$, 17.4, 1H), 5.69 (s, 1H), 5.64 (d, $J = 10.2$, 1H), 5.16–4.95 (m, 4H), 4.25 (d, $J = 10.2$, 1H), 4.00 (br s, 6H), 1.62 (br s, 6H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 144.2, 136.7, 135.6, 128.3, 128.1, 127.9, 127.9, 122.7, 120.7, 119.3, 118.9, 113.7, 113.3, 113.1, 109.1, 72.8, 66.4, 65.8, 58.9, 57.1, 30.7, 28.0, 27.8, 14.4; IR (thin film) 3517 w, 3447 w, 2936 w, 2880 w, 1724 s, 1513 m, 1456 m, 1397 w, 1336 w, 1314 m, 1218 m, 1193 m, 1049 s, 1021 s, 991 m, 912 w, 738 s; HRMS (EI): m/z calcd for $C_{29}H_{34}O_6N_2Na$ 529.2315, found 529.2297.

4.7. 3-Iodo-1-(2-methylbut-3-en-2-yl)-1*H*-indole 6

Indole **5** (7.37 g, 39.8 mmol) was dissolved in DMF (265 mL) and the reaction cooled to 0 °C. *N*-Iodosuccinimide (9.85 g, 43.8 mmol) was added in one portion and the reaction allowed to stir for 20 min. The reaction was judged complete by TLC, quenched with $NaHCO_3$, stirred for 10 min, diluted with H_2O, and extracted with Et_2O. The organic layers were combined, washed with H_2O and brine, dried over $MgSO_4$, and the solvent removed in vacuo. The residue was purified by flash silica gel chromatography eluting with 2.5% EtOAc–hexanes + 0.1% TEA to give an orange oil (10.75 g, 87%): TLC (5% EtOAc–hexanes) $R_f = 0.49$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49–7.47 (m, 1H), 7.44–7.42 (m, 1H), 7.36 (s, 1H), 7.16–7.15 (m, 2H), 6.14–6.08 (m, 1H), 5.24–5.15 (m, 2H), 1.74 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.6, 135.4, 131.7, 129.3, 121.8, 121.3, 120.1, 113.9, 113.9, 59.8, 55.2, 27.9; IR (thin film) 2979 m, 1504 w, 1450 s, 1412 w, 1366 w, 1305 s, 1229 s, 1184 s, 1018 w, 923 m, 740 s; HRMS (CI): m/z calcd for $C_{13}H_{14}NI$ 311.0171, found 311.0176.

4.8. (*R*)-3-(3-Iodo-1*H*-indol-1-yl)-3-methylbutane-1,2-diol 10

$K_2[OsO_2(OH)_4]$ (107 mg, 0.29 mmol), $(DHQD)_2$-PYR (320 mg, 0.36 mmol), $K_3Fe(CN)_6$ (28.67 g, 87.1 mmol), and K_2CO_3 (12.0 g, 87.1 mmol) were dissolved in 300 mL of 1:1 *tert*-butanol–H_2O. 3-Iodoindole **9** (9.03 g, 29.0 mmol) was added and the reaction stirred at room temperature for 24 h and judged to be complete

by TLC. $Na_2S_2O_3{\cdot}5H_2O$ (43.4 g, 175 mmol) was added and the reaction allowed to stir for 10 min. The resulting mixture was diluted with CH_2Cl_2 and H_2O and extracted. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent reduced in vacuo. The residue was purified by flash silica gel chromatography eluting with 40–80% EtOAc–hexanes + 0.1% TEA to yield a viscous, yellow oil (8.06 g, 80%, 91% ee by ^{19}F spectrum of the Mosher's ester): $[\alpha]_D^{20} = -3.3$ (*c* 1.0, $CHCl_3$); TLC (40% EtOAc–hexanes) $R_f = 0.30$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54–7.50 (m, 1H), 7.44–7.41 (m, 1H), 7.29 (s, 1H), 7.17–7.13 (m, 2H), 4.26 (t, $J = 4.0$, 1H), 3.29–3.25 (m, 2H), 2.75–2.70 (m, 1H), 2.27–2.23 (m, 1H), 1.68–1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.9, 1312.0, 130.4, 122.2, 121.8, 120.4, 113.4, 75.5, 62.4, 61.9, 55.9, 24.4, 24.1; IR (thin film) 3382 br s, 2985 m, 2942 m, 1603 w, 1448 s, 1303 s, 1222 s, 1191 s, 1088 s, 1030 s, 908 m, 738 s, HRMS (ES): *m*/*z* calcd for $C_{13}H_{16}INO_2Na$ 368.0123, found 368.0135.

4.9. (*R*)-3-Iodo-1-[2-(oxiran-2-yl)propan-2-yl]-1*H*-indole 11

Diol **10** (7.46 g, 22.2 mmol), TEA (6.1 mL, 43 mmol), and $Me_3N{\cdot}HCl$ (206 mg, 2.2 mmol) were dissolved in CH_2Cl_2 (43 mL) and cooled to 0 °C. TsCl (4.12 g, 21.6 mmol) was then added. The reaction was stirred at 0 °C for 20 min and judged to be complete by TLC. The reaction was diluted with MeOH (43 mL), K_2CO_3 (5.97 g, 43.2 mmol) then added, and the mixture allowed to warm to room temperature and stirred for 24 h. The solvent was reduced in vacuo and the residue dissolved in Et_2O and H_2O. The organic layer was separated, washed with brine, and then dried over $MgSO_4$. The solvent was reduced in vacuo. The residue was purified by flash silica gel chromatography (15% EtOAc–hexanes + 0.1% TEA) to yield a viscous, orange oil (5.96 g, 84% two steps): $[\alpha]_D^{20} = -3.6$ (*c* 1.0, $CHCl_3$); TLC (10% EtOAc–hexanes) $R_f = 0.28$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, $J = 8.4$, 1H), 7.45–7.43 (m, 1H), 7.38 (s, 1H), 7.24–7.17 (m, 2H), 3.26 (dd, $J = 2.9$, $J = 4.0$, 1H), 2.89 (t, $J = 4.14$, 1H), 2.76 (dd, $J = 2.8$, $J = 4.6$, 1H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 135.6, 131.7, 129.4, 122.4, 121.5, 120.4, 113.2, 58.7, 57.7, 56.1, 45.4, 24.4, 23.1; IR (thin film) 2983 m, 1450 s, 1305 s, 1226 m, 1190 s, 1018 w, 879 w, 741 s; HRMS (CI): *m*/*z* calcd for $C_{13}H_{14}INO$ 327.0120, found 327.0111.

4.10. Benzyl-(1*S*,2*R*)-2-hydroxy-1-(4″-methyl-2″,6″,7″-trioxabicyclo[2.2.2]octan-1″-yl)-2-[1-(2′-((*R*)-oxiran-2′-yl)propan-2′-yl)-1*H*-indol-3-yl]ethylcarbamate 12

3-Iodoindole **11** (12.14 g, 37.1 mmol) was dissolved in Et_2O (350 mL) and cooled to −78 °C. *n*-BuLi (10.0 M in hexane, 4.4 mL, 44 mmol) was added dropwise, and allowed to stir for 1 h. Freshly prepared $MgBr_2$ (6.83 g, 37.1 mmol) in Et_2O (40 mL) was added and allowed to stir for 1 h at −78 °C and then warmed to 0 °C. Serine aldehyde **7** (5.96 g, 18.56 mmol) in 100 mL of CH_2Cl_2 was added and the reaction allowed to stir for 30 min at 0 °C. The reaction was quenched with 5% NH_4Cl, diluted with Et_2O, washed with 5% NH_4Cl and brine, then dried over $MgSO_4$ and the solvent reduced in vacuo. An 88% de was calculated from integrating the α-proton of the crude product. The residue was purified by flash silica gel chromatography (5% CH_3CN–CH_2Cl_2 + 0.1% TEA) to give a pale yellow foam (2.07 g, 21%): $[\alpha]_D^{20} = -28.0$ (*c* 1.0, $CHCl_3$), TLC (1:1 EtOAc–hexanes) $R_f = 0.12$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, $J = 7.8$, 1H), 7.63 (d, $J = 8.3$, 1H), 7.29 (m, 5H), 7.26 (d, $J = 3.1$, 1H), 7.11 (m, 2H), 5.68 (s, 1H), 5.65 (d, $J = 10.2$, 1H), 5.12 (d, $J = 12.4$, 1H), 5.00 (d, $J = 12.4$, 1H), 4.25 (d, $J = 10.3$, 1H), 4.01 (m, 6H), 3.19 (d, $J = 1.97$, 1H), 3.14 (dd, $J = 2.9$, $J = 3.6$, 1H), 2.84 (t, $J = 4.3$, 1H), 2.73 (m, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 136.681, 135.8, 128.4, 128.2, 128.0, 127.9, 122.7, 121.3, 119.5, 119.3, 113.6, 112.9, 109.0, 72.8, 66.6, 65.6, 57.88, 57.61, 56.9, 45.6, 30.7, 23.8, 23.6, 14.4; IR (thin film) 3521 w, 2936 w, 2881 w, 1721 s, 1512 m, 1456 m, 1398 w, 1336 w, 1219 m, 1049 s, 734 s; HRMS (ES): *m*/*z* calcd for $C_{29}H_{34}N_2O_7Na$ 545.2264, found 545.2243.

4.11. Benzyl-(1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-(4″-methyl-2″,6″,7″-trioxabicyclo-[2.2.2]octan-1″-yl)-2-[1-(2′-((*R*)-oxiran-2′-yl)propan-2′-yl)-1*H*-indol-3-yl]ethylcarbamate 13

Compound **12** (551 mg, 1.1 mmol) and Proton Sponge® (678 mg, 3.2 mmol) were dissolved in CH_2Cl_2 (10.0 mL), *tert*-butyldimethylsilyltriflate (0.49 mL, 2.1 mmol) then added and the reaction stirred for 20 min at room temperature and judged to be complete by TLC. The reaction was diluted with H_2O and Et_2O and the layers separated. The organic layer was washed twice with 5% NH_4Cl, saturated $NaHCO_3$, brine, dried with $MgSO_4$, and the solvent was reduced in vacuo. Both diastereomers were visible by TLC and separated by flash silica gel chromatography (30% EtOAc–hexanes + 0.1% TEA) to yield a pale yellow foam (362.8 mg, 54%): $[\alpha]_D^{20} = -7.6$ (*c* 1.0, $CHCl_3$); TLC (30% EtOAc–hexane) $R_f = 0.26$; ^1H NMR ($CDCl_3$, 500 MHz, rotameric pairs are indicated where possible) δ 7.71–7.58 (m, 2H), 7.35–7.27 (m, 3H), 7.20–7.16 (m, 1H), 7.13–7.06 (m, 1H), 7.06–7.02 (m, 1H), 6.95 (t, $J = 7.7$, 0.5H), 6.45 (d, $J = 7.5$, 0.5H), [5.64–5.60 (major rot., m), 5.38 (minor rot., d, $J = 10.7$) 2H], [5.02–4.94 (major rot., m), 4.73 (minor rot., d, $J = 12.7$), 4.58 (minor rot., d, $J = 12.7$) 2H], 3.98–3.91 (m, 7H), [3.18–3.17 (major rot., m), 3.14–3.13 (minor rot., m) 1H], [2.83 (major rot., t, $J = 4.4$), 2.79 (minor rot., t, $J = 4.3$) 1H], [2.71–2.70 (major rot., m), 2.68–2.67 (minor rot., m) 1H], 1.58–1.51 (m, 6H), 0.90–0.82 (m, 12H), 0.04 (d, $J = 9.0$, 3H), −0.15 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, rotameric pairs are indicated where possible) δ [156.4 min., 156.3 maj.], 136.9, [136.1 min., 135.8 maj.], 128.4, 128.1, [127.9, 127.8], 127.3, 127.0, 126.7, 124.0, 123.2, [121.1 min., 121.0 maj.], 119.4, 119.1, 119.0, 118.9, [117.0 maj., 116.8 min.], [113.0 min., 112.7 maj.], 108.4, 107.9, [72.6, 72.5], [66.4 maj., 66.3 min.], [65.8 min., 65.8 maj.], [59.6 min., 59.4 maj.], 58.0, [57.6 min., 57.5 maj.], 45.6, 45.3, [30.6, 30.5], [25.8, 25.7], 24.3, 24.0, 23.9, 23.8, 23.4, 18.2, 14.4; IR (thin film)

3452 w, 2929 m, 2879 m, 1733 s, 1508 s, 1456 m, 1398 w, 1284 m, 1197 m, 1104 m, 1052 s, 1001 m, 838 m, 738 s; HRMS (ES): m/z calcd for $C_{35}H_{48}N_2O_7SiNa$ 659.3128, found 659.3137.

4.12. (2*S*,3*R*)-3″-Hydroxy-2″-(hydroxymethyl)-2″-methylpropyl-2-(benzyloxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-[1′-(2′-((*R*)-oxiran-2′-yl)propan-2′-yl)-1*H*-indol-3-yl]propanoate 14

Compound **13** (35.2 mg, 0.057 mmol) was dissolved in dioxane (0.25 mL) and glacial acetic acid (0.5 mL) added, followed by water (0.5 mL). The reaction was allowed to stir for 10 min until judged to be complete by TLC. Solvent was then removed in vacuo. The residue was purified by flash silica gel chromatography (3% MeOH–CH_2Cl_2) to give a pale yellow foam (26.1 mg, 72%): $[\alpha]_D^{20} = -5.5$ (c 1.0, $CHCl_3$); TLC (5% MeOH–CH_2Cl_2) $R_f = 0.35$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, $J = 8.4$, 1H), 7.64 (d, $J = 7.8$, 1H), 7.36–7.30 (m, 4H), 7.27 (s, 1H), 7.26–7.16 (m, 2H), 7.16–7.12 (m, 1H), 5.64 (d, $J = 8.5$, 1H), 5.58 (d, $J = 3.0$, 1H), 5.06–4.99 (m, 2H), 4.59 (dd, $J = 3.1$, $J = 8.5$, 1H), 4.20 (s, 2H), 3.52–3.41 (m, 4H), 3.25 (t, $J = 2.9$, 1H), 2.88 (t, $J = 4.3$, 1H), 2.73 (dd, $J = 2.7$, $J = 4.4$, 1H), 2.69 (br s, 1H), 2.64 (br s, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 0.87 (s, 9H), 0.79 (s, 3H), 0.01 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 156.5, 136.1, 135.8, 128.5, 128.3, 128.3, 127.1, 124.0, 121.6, 119.6, 119.0, 114.1, 113.2, 69.4, 67.7, 67.6, 67.5, 67.1, 60.1, 57.9, 45.4, 40.5, 25.7, 24.4, 23.3, 18.1, 16.8, −0.7, −5.5; IR (thin film) 3443 m, 2953 m, 2856 m, 1722 s, 1506 m, 1457 m, 1255 s, 1199 s, 1058 s, 837 s, 740 s; HRMS (ES): m/z calcd for $C_{35}H_{50}O_8N_2$-SiNa 677.3234, found 677.3240.

4.13. (2*S*,3*R*)-Methyl 2-(benzyloxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-[1′-(2′-((*R*)-oxiran-2′-yl)propan-2′-yl)-1*H*-indol-3-yl]propanoate 15

Compound **14** (58.5 mg, 0.089 mmol) was dissolved in dioxane (1.0 mL), THF (1.0 mL), and water (1.0. mL). 1.0 M LiOH (0.14 mL) was added to the solution and the reaction stirred at room temperature for 3 h until judged complete by TLC. The reaction was acidified to pH 5 with 1.0 N HCl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and the solvent removed in vacuo. The resulting crude free acid was then dissolved in MeOH (0.5 mL) and TMS-diazomethane (2.0 M in hexanes, 11 mL) added. The reaction was allowed to stir for 10 min. Solvent was removed in vacuo, and the residue purified by flash silica gel chromatography (25% AcOEt–hexanes) to give a pale, yellow oil (17.1 mg, 88% for two steps): $[\alpha]_D^{20} = -8.2$ (c 2.1, $CHCl_3$); TLC (30% AcOEt–Hex) $R_f = 0.51$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68–7.64 (m, 2H), 7.33–7.30 (m, 4H), 7.29 (s, 1H), 7.26–7.19 (m, 2H), 7.18–7.10 (m, 1H), 5.65–5.63 (m, 2H), 4.98 (d, $J = 2.0$, 2H), 4.58 (dd, $J = 2.0$, $J = 9.4$, 1H), [rotamer pair: 3.79 (s, 2H), 3.75 (s, 1H)], 3.22 (t, $J = 3.5$, 1H), 2.87 (t, $J = 4.0$, 1H), 2.71 (t, $J = 2.7$, 1H), [rotamer pair: 1.62 (s, 3H), 1.59 (s, 3H)], 0.93–0.86 (m, 9H), [rotamer pair: 0.00 (s), −0.01 (s), 3H], [rotamer pair: −0.1 (s), −0.2 (s), 3H]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 156.7, 136.8, 136.2, 128.9, 128.7, 128.6, 128.6, 124.3, 121.9, 119.9, 119.5, 114.8, 113.6, 69.9, 67.3, 60.7, 58.4, 52.8, 45.9, 26.1, 24.7, 23.9, 18.5, −4.2, −5.1; IR (thin film) 2929 m, 2856 w, 1728 s, 1507 m, 1456 m, 1317 w, 1253 m, 1201 m, 1063 m, 836 m, 778 m, 740 m; HRMS (ES): m/z calcd for $C_{31}H_{42}N_2O_6SiNa$ 589.2709, found 589.2713.

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