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Construction of the Pentacyclic Core and Formal Total Synthesis of (*rac*)-Renieramycin T

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A formal total synthesis of the antitumor marine natural product (*rac*)-renieramycin T, which possesses a characteristic ecteinascidin-type A ring in the renieramycin–saframycin core skeleton, was elaborated. The key steps in the synthesis of (*rac*)-renieramycin T are a modified Pictet–Spengler cyclization of dialkylated oxomalonate derivatives and decarboxylation via a monocarboxylic acid derivative followed by stereocontrolled protonation of the enol intermediate. A key intermediate in our previous synthesis of renieramycin T was used, and the formal synthesis was accomplished in 21 steps from a known piperazine-2,5-dione derivative.

1. Introduction

Many 1,2,3,4-tetrahydroisoquinolines exhibit various bioactivities, such as antitumor, antibacterial, antiviral, anticoagulant, anti-inflammatory, anti-Alzheimer, and anticonvulsant activities.[1] Among them, members of the saframycin, renieramycin, and ecteinascidin families have captured intense attention due to their interesting biological activities and intriguing structures (Figure 1). Particularly, novel marine-derived ecteinascidin 743[2] (**2**, Trabectedin, Yondelis) has superior antitumor activity and was approved by the European Commission in 2007[3] and the US Food and Drug Administration (FDA) in 2015[4] for the treatment of soft-tissue sarcomas.

A large number of renieramycin marine natural products[5] have been discovered in sponges of genera *Reniera*,[6] *Xestospongia*,[7] *Haliclona*,[8] *Cribrochalina*,[9] and *Neopetrosia*[10] in miniscule amounts. In our continuing chemical studies on renieramycins,[11] we found that the transformation of an unstable aminal group in a natural product, such as renieramycin E (**1a**), into an aminonitrile group by pretreatment with KCN prior to extraction and isolation furnished many kinds of stable renieramycin derivatives, such as renieramycin M (**1b**).[12] We also elucidated the chemical structure of renieramycin T (**1c**), which was isolated from the blue sponge *Xestospongia* sp. in Thailand[11c] and the Philippines.[11b] Renieramycin T (**1c**) possesses a highly substituted phenol in the terminal A ring and a condensed 1,3-dioxole ring, which are exactly the same as

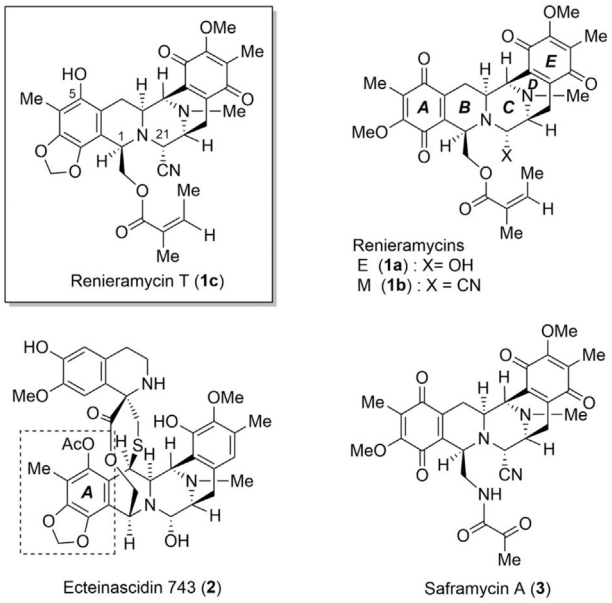

Figure 1. Structures of 1,2,3,4-tetrahydroisoquinoline natural products.

those in ecteinascidins. As the chemical structure of **1c** is the first example of a hybrid pentacyclic core, we are very interested in the biosynthetic pathway and the biological activity of **1c** and its derivatives. To date, two total syntheses of (−)-**1c** by us and Chen's group have been reported.[13] However, we focused on an alternative route for supplying a large amount of **1c** to promote research of structure–activity relationships. Herein, we report a formal total synthesis of **1c**, which includes the Pictet–Spengler reaction of a primary amine with an oxomalonic acid ester followed by decarboxylation and stereocontrolled protonation at C1 of the enol intermediate from the less-hindered face.[14]

2. Results and Discussion

We embarked on an alternative total synthesis of **1c** on the basis of our previous synthetic studies on saframycin antitumor

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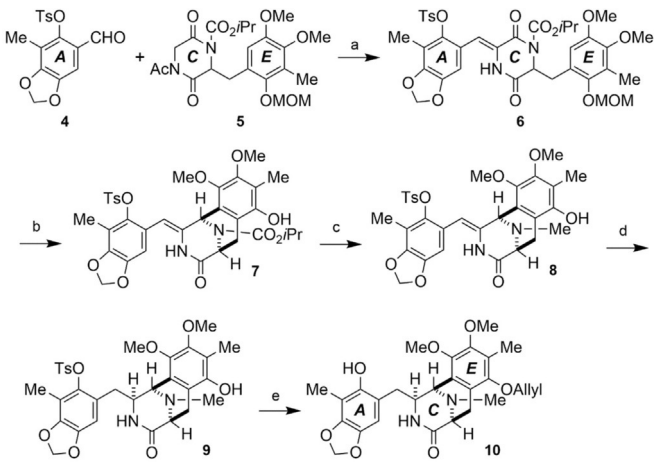
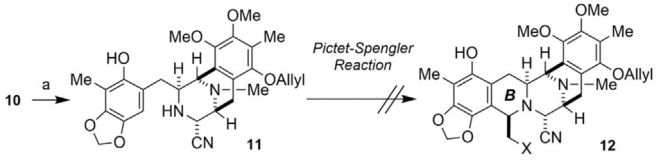
antibiotics (Scheme 1).[15] Condensation of highly functionalized benzaldehyde **4**[16] with known piperazine-2,5-dione derivative **5**[15b] afforded *Z* isomer **6** in 79% yield. Chemoselective reduction of the carbonyl group activated by an isopropyloxycarbonyl group in **6**, followed by treatment with trifluoroacetic acid (TFA) gave cyclized product **7** (78%, two steps). Removal of the isopropoxycarbonyl group in **7** with TFA and H_2SO_4 gave a secondary amine that was treated with a $NaBH_3CN$–aqueous formaldehyde system to provide tertiary amine **8** in 68% overall yield. Hydrogenation (2.8 MPa) of the *exo* olefin in **8** on 20% $Pd(OH)_2$ in EtOH at 80 °C along with hydrogen attack from the less-hindered α face gave **9** as a single isomer in 77% yield. At that point, we thought it would be important to distinguish the two phenolic OH groups in both terminal rings, because regioselective oxidation was required to prepare *p*-quinone in the E ring phenol at a later stage. Thus, the phenolic OH group of the E ring of **9** was protected with an allyl group, and the tosyl group in the A ring was removed with KOH/H_2O to increase its reactivity for the Pictet–Spengler cyclization to give **10** in 80% over two steps.



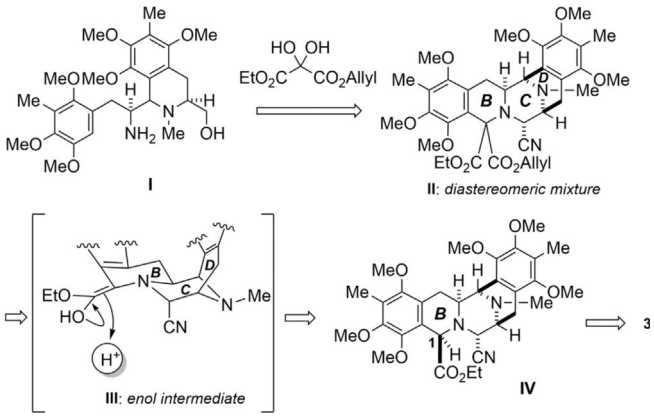
Scheme 1. Preparation of tricyclic lactam **10**. Reagents and conditions: a) *t*BuOK, *t*BuOH, CH_2Cl_2, 0 °C, 1 h, 79%; b) 1) $Li(tBuO)_3AlH$, THF, 25 °C, 6 h; 2) TFA, CH_2Cl_2, 25 °C, 3 h, 78% (two steps); c) 1) H_2SO_4, TFA, anisole, 25 °C, 7.5 h; 2) $NaBH_3CN$, 37% aq HCHO, MeOH, AcOH, 25 °C, 2 h, 68% (two steps); d) H_2 (2.8 MPa), 20% $Pd(OH)_2/C$, EtOH, 80 °C, 27 h, 77%; e) 1) allyl bromide, K_2CO_3, acetone, reflux, 5.5 h; 2) aq KOH, EtOH, reflux, 3 h, 80% (two steps). Ts = tosyl, Ac = acetyl, MOM = methoxymethyl.

With precursor **10** in hand, we focused on the construction of a pentacyclic core by using the Pictet–Spengler cyclization (Scheme 2). Partial reduction of the lactam carbonyl group in **10**, followed by the introduction of a cyanide group gave aminonitrile **11**. We had hoped that the aminonitrile would be more reactive than lactam **10** in the Pictet–Spengler cyclization. However, it was revealed that the Pictet–Spengler cyclization of **11** with even commonly used simple aldehydes,[15c] for example, the reaction of **11** with benzoyloxyacetaldehyde, did not proceed at all.[17] Furthermore, substrate decomposition was observed if harsher reaction conditions were used. It was clarified that the aminonitrile moiety of **11** was relatively unstable under acidic or high-temperature conditions. Therefore, we abandoned this route at this stage.



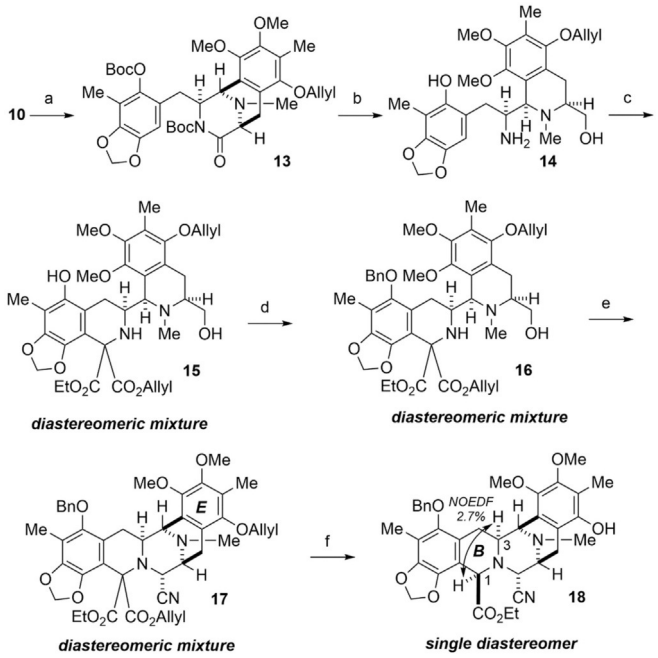
Scheme 2. Cyclization attempt by using the Pictet–Spengler reaction of aminonitrile **11**. Reagents and conditions. a) Cp_2ZrHCl, THF, −20 to 0 °C, 1 h; aq KCN, 25 °C, 4 h, 96%. Cp = η^5-cyclopentadienyl.

This problem was solved by applying our protocol to the total synthesis of saframycin A (**3**, Scheme 3).[18] Primary amine **I** did not have a relatively unstable aminonitrile group, and so steric repulsion would be reduced. Thus, it would be easy to construct desired pentacyclic core **IV** by using a three-step sequence through compound **II**, which includes the Pictet–Spengler cyclization with oxomalonic acid ester to install a diester unit, decarboxylation, and stereoselective protonation from the convex face of these "V"-shaped bis-1,2,3,4-tetrahydroisoquinoline natural products.



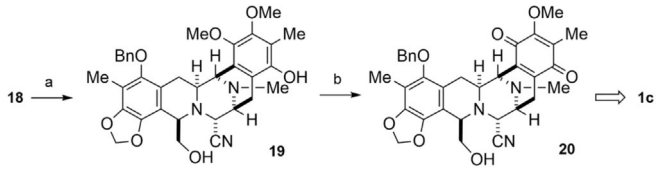
Scheme 3. Recently established strategy for construction of the B ring of bis-tetrahydroisoquinoline natural products, represented by saframycin A (**3**).

Activation of the lactam carbonyl group in **10** with di-*tert*-butyl dicarbonate (Boc_2O) gave **13** in 72% yield according to a protocol independently outlined by Fukuyama and Stoltz[19] (Scheme 4). Reductive cleavage of the lactam ring in **13** with $NaBH_4$ in EtOH, followed by treatment with TFA in CH_2Cl_2 gave primary amine **14** (73%, two steps). Pictet–Spengler cyclization of **14** with allyl ethyl oxomalonate hydrate[20] furnished diester **15** as an inseparable diastereomeric mixture (1:1) in 80% yield. Then, the phenolic OH group in **15** was protected by a benzyl (Bn) group (83%), and Swern oxidation of **16** followed by treatment with KCN afforded pentacyclic core **17** (56%, two steps). Removal of the allyl group in **17** with $Pd(PPh_3)_4$ and dimedone, followed by decarboxylation exclusively gave ester **18** as a single diastereomer in 72% yield.[21,22] The stereochemistry of **18** was determined by nuclear Overhauser enhancement (NOE) experiments, which indicated that **18** had a *syn* relationship between the C1 and C3 diaxial protons.



Scheme 4. Construction of the B ring. Reagents and conditions. a) Boc_2O, 4-(dimethylamino)pyridine (DMAP), MeCN, reflux, 57.5 h, 72%; b) 1) $NaBH_4$, EtOH, 25 °C, 3 h; 2) TFA, CH_2Cl_2, 25 °C, 1.5 h, 73% (two steps); c) 1-allyl 3-ethyl 2,2-dihydroxymalonate, TFA, AcOH, 25 °C, 6 h, 80%; d) BnBr, K_2CO_3, acetone, 25 °C, 8 h, 83%; e) 1) Swern oxidation; 2) aq KCN, AcOH, THF, 25 °C, 2 h, 56% (two steps); f) 1) $Pd(PPh_3)_4$, dimedone, THF, 25 °C, 1 h; 2) $CHCl_3$, reflux, 2 h, 72% (two steps).

Finally, reduction of ester **18** (71%), followed by oxidative demethylation of **19** into quinone ring afforded **20** (51%) (Scheme 5). This is the key intermediate in our total synthesis;[13a] its ^1H NMR, ^{13}C NMR, and IR spectroscopy data; MS data; and TLC behavior were identical to those of an authentic sample upon comparison Thus, we accomplished a formal synthesis of (*rac*)-renieramycin T (**1 c**).



Scheme 5. Formal synthesis of (*rac*)-renieramycin T (**1 c**). Reagents and conditions. a) $LiBH_4$, MeOH, THF, 25 °C, 3 h, 71%; b) aq ceric ammonium nitrate (CAN), THF, 0 °C, 20 min, 51%.

3. Conclusions

We accomplished a formal synthesis of (*rac*)-renieramycin T (**1 c**). Whereas the aromatic ring having a 1,3-dioxole ring suppressed reactivity during the Pictet–Spengler cyclization, reductive cleavage of the lactam ring in **13** afforded primary amine **14**. Then, treatment of **14** with allyl ethyl oxomalonate in the Pictet–Spengler reaction, followed by decarboxylation and stereoselective protonation of the resulting enol intermediate from the less-hindered face produced the desired bis-1,2,3,4-tetrahydroisoquinoline intermediate.

Ways of utilizing this strategy for the synthesis of ecteinascidins along with fennebricin B[23] are under investigation in our laboratory.

Experimental Section

General Methods

All reactions involving air- and moisture-sensitive reagents were performed in oven-dried glassware and by using standard syringe-septum cap techniques. All reactions were monitored by thin-layer chromatography (silica gel GF_{254}) examined under UV light ($\lambda =$ 254 nm). Flash column chromatography was performed on Merck Silica Gel (230–400 mesh) with the solvent indicated. IR spectra were obtained with a Shimadzu Prestige-21/IR Affinity-1 Fourier Transform Infrared (FTIR) spectrometer. ^1H NMR and ^{13}C NMR spectroscopic data were recorded with a JEOL ECS-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C and with a JEOL AL-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C. NMR spectra were measured in $CDCl_3$, and the chemical shifts were recorded in δ_H values relative to $(CH_3)_4Si$ as the internal standard. Low- and high-resolution mass (HRMS) mass spectra were recorded with a JMS-700 instrument with a direct inlet system operating at 70 eV.

Syntheses

(Z)-Isopropyl 2-[4,5-dimethoxy-2-(methoxymethoxy)-3-methylbenzyl]-5-{[7-methyl-6-(tosyloxy)benzo[d][1,3]dioxol-5-yl]methylene}-3,6-dioxopiperazine-1-carboxylate (6)

A solution of *t*BuOK in *t*BuOH (1 M, 30 mL, 30 mmol) was added dropwise to a stirred solution of aldehyde **4** (8.36 g, 25 mmol) and acetate **5** (11.66 g, 25 mmol) in CH_2Cl_2 (100 mL) at 0 °C over 1 h, and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with saturated aqueous NH_4Cl solution (200 mL) and extracted with CH_2Cl_2 (3×250 mL). The combined extract was washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (18.26 g), which was subjected to flash column chromatography on SiO_2 (500 g) with hexane/EtOAc (3:2) to afford **6** (14.62 g, 79%) as a colorless amorphous powder; $R_f = 0.35$ (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 8.5$ Hz, 2H, $C_6H_4CH_3$), 7.24 (d, $J = 8.5$ Hz, 2H, $C_6H_4CH_3$), 7.10 (br s, 1H, *NH*), 6.41 (s, 1H, 4″-H), 6.34 (s, 1H, 6′-H), 6.15 (s, 1H, 5a-H), 6.07 (d, $J = 1.2$ Hz, 1H, 2″-H), 6.05 (d, $J = 1.2$ Hz, 1H, 2″-H), 5.17 (sept, $J = 5.7$ Hz, 1H, $CH(CH_3)_2$), 5.03 (t, $J = 4.9$ Hz, 1H, 2-H), 4.88 (d, $J = 5.9$ Hz, 1H, OCH_2OCH_3), 4.82 (d, $J = 5.9$ Hz, 1H, OCH_2OCH_3), 3.73 (s, 3H, 5′-OCH_3), 3.58 (s, 3H, OCH_2OCH_3), 3.53 (s, 3H, 4′-OCH_3), 3.30 (d, $J = 4.9$ Hz, 2H, 2a-H_2), 2.34 (s, 3H, $C_6H_4CH_3$), 2.27 (s, 3H, 7″-CH_3), 2.00 (s, 3H, 3′-CH_3), 1.43 (d, $J = 5.7$ Hz, 3H, $CH(CH_3)_2$), 1.41 ppm (d, $J = 5.7$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.9$ (C-3), 157.4 (C-6), 152.2 (CO_2), 149.5 (C-2′ or 5′), 149.3 (C-2′ or 5′), 148.1 (C-4′ or 7″a), 148.0 (C-4′ or 7″a), 145.6 (C-3″a), 145.4 ($C_6H_4CH_3$), 141.8 (C-6″), 132.3 ($C_6H_4CH_3$), 130.1 ($C_6H_4CH_3$), 128.7 ($C_6H_4CH_3$), 125.9 (C-3′), 124.7 (C-5), 122.3 (C-1′), 119.7 (C-5″), 117.1 (C-7″), 113.9 (C-5a), 112.9 (C-6′), 104.6 (C-4″), 102.3 (C-2″), 100.0 (CH_2OCH_3), 72.0 ($CH(CH_3)_2$), 60.1 (4′-OCH_3), 59.9 (C-2), 57.6 (CH_2OCH_3), 55.8 (5′-OCH_3), 33.8 (C-2a), 21.8 ($CH(CH_3)_2$), 21.8 ($CH(CH_3)_2$), 21.5 ($C_6H_4CH_3$), 10.9 (7″-CH_3), 10.4 ppm (3′-CH_3); FTIR (KBr): $\tilde{\nu} = 1773$, 1694, 1479, 1420, 1375, 1281, 1233, 1196, 1173, 1103, 1080, 1061, 1022, 972, 806 cm^{-1}; MS (EI): *m/z* (%): 741 (40), 740 (100) $[M]^+$, 569 (33), 568 (31), 499 (31), 467 (55), 319 (21), 287 (59), 230 (27), 225 (43), 220 (23), 219 (46), 191 (23), 190 (22), 181

(73); HRMS (EI): *m/z*: calcd for $C_{36}H_{40}O_{13}N_2S$: 740.2251 $[M]^+$; found: 740.2250.

(Z)-Isopropyl (1R,5S*)-7-hydroxy-9,10-dimethoxy-8-methyl-2-{[7-methyl-6-(tosyloxy)-benzo[d][1,3]dioxol-5-yl]methylene}-4-oxo-1,2,3,4,5,6-hexahydro-1,5-iminobenzo[d]azocine-11-carboxylate (7)*

Li(*t*BuO)$_3$AlH (6.36 g, 25 mmol) was added to a stirred solution of **6** (3.70 g, 5 mmol) in THF (170 mL) at 0 °C over 40 min, and the mixture was stirred at 25 °C for 6 h. The mixture was diluted by adding a saturated aqueous Rochelle salt solution (100 mL) and was then extracted with $CHCl_3$ (3×300 mL). The combined extract was washed with brine (300 mL), dried, and concentrated in vacuo to give a residue, which was used in the next step without further purification. TFA (22.5 mL) was added to a stirred solution of the above product (3.71 g) in CH_2Cl_2 (45 mL), and the mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuo, and the residue was diluted with H_2O (200 mL). Then, the mixture was brought to pH 9 with concd. NH_4OH (25 mL) and was extracted with CH_2Cl_2 (3×300 mL). The combined extract was washed with brine (300 mL), dried, and concentrated in vacuo to give a residue (3.75 g), which was subjected to column chromatography on SiO_2 (100 g) with $CHCl_3$/EtOAc (4:1) to afford tricyclic lactam **7** (2.64 g, 78%, two steps) as a pale-yellow amorphous powder. As it was a mixture of rotational isomers, the ^{1}H NMR and ^{13}C NMR spectra are both extremely complex at 25 °C in $CDCl_3$; R_f=0.23 ($CHCl_3$/EtOAc 4:1); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 100 °C): δ=8.67 (s, 1H, *O*H or *N*H), 7.99 (s, 1H, *O*H or *N*H), 7.74 (d, *J*=8.0 Hz, 2H, $C_6H_4CH_3$), 7.44 (d, *J*=8.0 Hz, 2H, $C_6H_4CH_3$), 6.57 (s, 1H, 4′-H), 6.02 (s, 2H, 2′-H$_2$), 5.72 (s, 1H, 1-H), 5.65 (s, 1H, 2a-H), 4.89 (sept, *J*=5.3 Hz, 1H, C*H*(CH$_3$)$_2$), 4.81 (dd, *J*=5.2, 2.3 Hz, 1H, 5-H), 3.77 (s, 3H, 10-OCH$_3$), 3.72 (s, 3H, 9-OCH$_3$), 2.92 (d, *J*=2.3 Hz, 1H, 6-Hα), 2.91 (d, *J*=5.2 Hz, 1H, 6-Hβ), 2.44 (s, 3H, $C_6H_4CH_3$), 2.07 (s, 3H, 8-CH$_3$), 1.99 (s, 3H, 7′-CH$_3$), 1.25 (d, *J*=5.3 Hz, 3H, CH(C*H*$_3$)$_2$), 1.24 ppm (d, *J*=5.3 Hz, 3H, CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 100 °C): δ=167.6 (C-1), 152.5 (CO_2), 149.1 (C-7 or 9), 148.3 (C-7 or 9), 145.4 (C-7′a), 145.1 ($C_6H_4CH_3$), 144.6 (C-3′a), 142.5 (C-10a), 139.6 (C-6′), 133.9 (C-2 or 5′ or 7′), 132.4 ($C_6H_4CH_3$), 129.4 ($C_6H_4CH_3$), 127.5 ($C_6H_4CH_3$), 124.0 (C-8 or 6a or 10a), 121.7 (C-2 or 5′ or 7′), 118.5 (C-8 or 6a or 10a), 114.8 (C-8 or 6a or 10a), 114.0 (C-2 or 5′ or 7′), 106.0 (C-4′), 101.3 (C-2′), 101.2 (C-2a), 68.8 (CH(CH$_3$)$_2$), 59.5 (10-OCH$_3$), 59.2 (9-OCH$_3$), 51.6 (C-5), 48.8 (C-1), 26.0 (C-6), 21.2 (CH(CH$_3$)$_2$), 21.2 (CH(CH$_3$)$_2$), 20.6 ($C_6H_4CH_3$), 9.8 (7′-CH$_3$), 8.7 ppm (8-CH$_3$); FTIR (KBr): $\tilde{\nu}$=3379, 1684, 1476, 1458, 1420, 1373, 1352, 1298, 1275, 1248, 1217, 1192, 1180, 1167, 1109, 1078, 1024, 1001, 816, 808 cm^{-1}; MS (EI): *m/z* (%): 680 (13) $[M]^+$, 526 (41), 525 (100), 440 (23), 439 (92), 221 (13), 220 (54), 205 (11); HRMS (EI): *m/z*: calcd for $C_{34}H_{36}O_{11}N_2S$: 680.2040 $[M]^+$; found: 680.2039.

(Z)-{(1R,5S*)-1,2,3,4,5,6-Hexahydro-2-[7-hydroxy-9,10-dimethoxy-8,11-dimethyl-4-oxo-3,4,5,6-tetrahydro-1,5-iminobenzo-[d]azocin-2(1H)-ylidene]methyl}-4-methylbenzo-[d][1,3]-dioxol-5-yl 4-methylbenzenesulfonate (8)*

Anisole (1.1 mL, 10 mmol) and concd. H_2SO_4 (2.4 mL) were successively added to a stirred solution of **7** (1.36 g, 2 mmol) in TFA (47.6 mL) at 0 °C, and the mixture was stirred at 25 °C for 7.5 h. After the mixture was diluted with H_2O (800 mL) at 0 °C, it was made alkaline with concd. NH_4OH (75 mL) and was then extracted with $CHCl_3$ (2×700 mL) and, finally, $CHCl_3$/MeOH (9:1, 2×700 mL). The combined extract was dried and concentrated in vacuo to give a residue, which was used in the next step without further purification. An analytical sample of the secondary amine was obtained as a yellow amorphous powder by column chromatography with EtOAc/MeOH (19:1); R_f=0.39 (EtOAc/MeOH 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.77 (d, *J*=8.3 Hz, 2H, $C_6H_4CH_3$), 7.33 (d, *J*=8.3 Hz, 2H, $C_6H_4CH_3$), 7.22 (br s, 1H, *N*H), 6.42 (s, 1H, 4′-H), 5.97 (d, *J*=1.1 Hz, 1H, 2′-H), 5.96 (d, *J*=1.1 Hz, 1H, 2′-H), 5.71 (s, 1H, 2a-H), 4.77 (s, 1H, 1-H), 3.98 (br s, 1H, 5-H), 3.85 (s, 3H, 10-OCH$_3$), 3.78 (s, 3H, 9-OCH$_3$), 3.01–2.92 (overlapped, 2H, 6-H$_2$), 2.46 (s, 3H, $C_6H_4CH_3$), 2.14 (s, 3H, 8-CH$_3$), 1.94 ppm (s, 3H, 7′-CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.4 (C-4), 149.7 (C-9), 148.0 (C-7), 146.4 (C-7′a), 145.6 (C-5′), 145.4 (C-3′), 143.8 (C-10), 140.8 (C-6′), 136.9 (C-2), 134.1 ($C_6H_4CH_3$), 129.7 ($C_6H_4CH_3$), 128.2 ($C_6H_4CH_3$), 125.6 (C-6a or 10a), 121.9 ($C_6H_4CH_3$), 117.7 (C-8), 115.5 (C-7′), 114.6 (C-6a or 10a), 106.1 (C-4′), 101.9 (C-2′), 101.3 (C-2a), 60.2 (10-CH$_3$), 60.1 (9-OCH$_3$), 52.4 (C-5), 48.8 (C-1), 27.0 (C-6), 21.7 ($C_6H_4CH_3$), 10.5 (7′-CH$_3$), 8.8 ppm (8-CH$_3$); FTIR (KBr): $\tilde{\nu}$=3305, 1670, 1476, 1460, 1418, 1350, 1219, 1192, 1179, 1076 cm^{-1}; MS (EI): *m/z* (%): 594 (8) $[M]^+$, 440 (31), 439 (100), 221 (13), 220 (50); HRMS (EI): *m/z*: calcd for $C_{30}H_{30}O_9N_2S$: 594.1672 $[M]^+$; found: 594.1669.

A 37% aqueous solution of formaldehyde (8 mL), $NaBH_3CN$ (1.51 g, 24 mmol), and AcOH (26.3 mL) were successively added to a stirred solution of the above product (1.00 g) in MeOH (100 mL) at 0 °C, and the mixture was then stirred at 25 °C for 2 h. The mixture was diluted with H_2O (200 mL), it was made alkaline with concentrated NH_4OH (40 mL) and extracted with $CHCl_3$ (3×300 mL). The combined extract was washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (2.92 g), which was subjected to column chromatography on SiO_2 (60 g) with hexane/EtOAc (13:7) to afford **8** (833.8 mg, 68%, two steps) as a colorless amorphous powder; R_f=0.23 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.73 (d, *J*=8.5 Hz, 2H, $C_6H_4CH_3$), 7.30 (d, *J*=8.5 Hz, 2H, $C_6H_4CH_3$), 6.44 (s, 1H, 4′-H), 5.96 (s, 2H, 2′-H$_2$), 5.78 (s, 1H, 2a-H), 4.83 (br s, 1H, *N*H), 4.53 (s, 1H, 1-H), 3.85 (s, 3H, 10-OCH$_3$), 3.78 (s, 3H, 9-OCH$_3$), 3.64 (d, *J*=7.2 Hz, 1H, 5-H), 3.07 (dd, *J*=17.0, 7.2 Hz, 1H, 6-Hα), 2.93 (d, *J*=17.0 Hz, 1H, 6-Hβ), 2.56 (s, 3H, *N*CH$_3$), 2.46 (s, 3H, $C_6H_4CH_3$), 2.15 (s, 3H, 8-CH$_3$), 1.92 ppm (s, 3H, 7′-CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.9 (C-4), 149.8 (C-9), 147.7 (C-7), 146.4 (C-7′a), 145.6 (C-3′a or $C_6H_4CH_3$), 145.4 (C-3′a or $C_6H_4CH_3$), 143.9 (C-10), 140.6 (C-6′), 134.6 (C-2 or 6a), 133.7 ($C_6H_4CH_3$), 129.8 ($C_6H_4CH_3$), 128.3 ($C_6H_4CH_3$), 126.0 (C-10a), 122.3 (C-5′), 117.1 (C-8), 115.8 (C-7′), 113.9 (C-2 or 6a), 106.2 (C-4′), 103.9 (C-2a), 101.9 (C-2′), 60.3 (10-OCH$_3$), 60.2 (9-OCH$_3$), 59.1 (C-5), 55.5 (C-1), 41.5 (*N*CH$_3$), 26.7 (C-6), 21.7 ($C_6H_4CH_3$), 10.4 (7′-CH$_3$), 8.7 ppm (8-CH$_3$); FTIR (KBr): $\tilde{\nu}$=1476, 1460, 1418, 1371, 1352, 1215, 1192, 1179, 1165, 1115, 1078, 1063 cm^{-1}; MS (EI): *m/z* (%): 608 (7) $[M]^+$, 454 (28), 453 (100), 235 (14), 234 (47); HRMS (EI): *m/z*: calcd for $C_{31}H_{32}O_9N_2S$: 608.1829 $[M]^+$; found: 608.1829.

{(1R,2S*,5S*)-[7-Hydroxy-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-iminobenzo[d]azocin-2-yl]-methyl}-4-methylbenzo[d][1,3]dioxol-5-yl 4-methylbenzene-sulfonate (9)*

A suspension of **8** (608.7 mg, 1 mmol) in EtOH (25 mL) was hydrogenated over 20% Pd(OH)$_2$ on carbon (280.9 mg) at 80 °C for 27 h under a hydrogen atmosphere (2.8 MPa). The catalyst was removed by filtration, and the residue trapped by the filter paper was washed with $CHCl_3$ and MeOH. The combined filtrate was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (15 g) with EtOAc/MeOH (9:1) to afford **9** (472.3 mg, 77%) as a colorless amorphous powder; R_f=0.23

(EtOAc/MeOH 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.0 Hz, 2H, $C_6H_4CH_3$), 7.33 (d, J = 8.0 Hz, 2H, $C_6H_4CH_3$), 6.49 (s, 1H, 4′-H), 5.97 (d, J = 1.5 Hz, 1H, 2′-H), 5.96 (d, J = 1.5 Hz, 1H, 2′-H), 4.21–4.14 (overlapped, 2H, 1-H & 2-H), 3.83 (s, 3H, 10-OCH_3), 3.82 (s, 3H, 9-OCH_3), 3.59 (d, J = 7.2 Hz, 1H, 5-H), 3.48 (dd, J = 14.6, 2.4 Hz, 1H, 2a-Hα), 2.96 (dd, J = 17.2, 7.2 Hz, 1H, 6-Hα), 2.78 (d, J = 17.2 Hz, 1H, 6-Hβ), 2.47 (s, 3H, $C_6H_4CH_3$), 2.45 (s, 3H, NCH_3), 2.24–2.15 (overlapped, 1H, 2a-Hβ), 2.19 (s, 3H, 8-CH_3), 1.95 ppm (s, 3H, 7′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C-4), 149.8 (C-9), 147.9 (C-7), 146.1 (C-7′a), 145.7 (C-3′a), 145.3 ($C_6H_4CH_3$), 144.8 (C-10), 141.2 (C-6′), 133.7 ($C_6H_4CH_3$), 129.9 ($C_6H_4CH_3$), 127.9 ($C_6H_4CH_3$), 124.6 (C-5′), 121.8 (C-6a or 10a), 117.5 (C-8), 115.4 (C-7′), 114.6 (C-6a or 10a), 107.5 (C-4′), 101.8 (C-2′), 60.5 (9-OCH_3), 60.2 (10-OCH_3), 58.1 (C-5), 55.9 (C-2), 54.4 (C-1), 40.1 (NCH_3), 33.3 (C-2a), 23.1 (C-6), 21.8 ($C_6H_4CH_3$), 10.6 (7′-CH_3), 8.9 ppm (8-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3364, 2936, 1736, 1661, 1476, 1456, 1418, 1344, 1194, 1180, 1076, 1055 cm^{-1}; MS (EI): m/z (%): 610 (9) $[M]^+$, 456 (10), 455 (19), 235 (28), 234 (100); HRMS (EI): m/z: calcd for $C_{31}H_{34}O_9N_2S$: 610.1985 $[M]^+$; found: 610.1987.

(1R,2S*,5S*)-7-(Allyloxy)-2-[(6-hydroxy-7-methylbenzo[d]-[1,3]dioxol-5-yl)methyl]-9,10-dimethoxy-8,11-dimethyl-2,3,5,6-tetrahydro-1,5-iminobenzo[d]azocin-4(1H)-one (10)*

A solution of **9** (1.36 g, 2.23 mmol) in acetone (110 mL) was stirred in the presence of K_2CO_3 (1.55 g, 11.14 mmol) at 0 °C, allyl bromide (385 μL, 4.45 mmol) was added over 10 min, and the mixture was heated at reflux for 5.5 h. The mixture was filtered, and the combined filtrate was concentrated in vacuo to give a residue, which was used in the next step without further purification. An analytical sample was obtained as a colorless amorphous powder by column chromatography with EtOAc to EtOAc/MeOH (19:1); R_f = 0.21 ($CHCl_3$/MeOH 97:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.5 Hz, 2H, $C_6H_4CH_3$), 7.34 (d, J = 8.5 Hz, 2H, $C_6H_4CH_3$), 6.50 (s, 1H, 4′-H), 6.09 (ddt, J = 17.2, 10.7, 5.4 Hz, 1H, $OCH_2CH{=}CH_2$), 5.96 (d, J = 1.2 Hz, 1H, 2′-H), 5.95 (d, J = 1.2 Hz, 1H, 2′-H), 5.45 (dq, J = 17.2, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 5.27 (dq, J = 10.7, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 5.20 (s, 1H, *N*H), 4.33 (ddt, J = 12.7, 5.4, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.28 (ddt, J = 12.7, 5.4, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.20–4.15 (overlapped, 2H, 1-H and 2-H), 3.87 (s, 3H, 10-OCH_3), 3.82 (s, 3H, 9-OCH_3), 3.54 (d, J = 7.1 Hz, 1H, 5-H), 3.45 (dd, J = 14.4, 1.7 Hz, 1H, 2a-Hα), 3.07 (dd, J = 18.0, 7.1 Hz, 1H, 6-Hα), 2.95 (d, J = 18.0 Hz, 1H, 6-Hβ), 2.47 (s, 6H, $C_6H_4CH_3$ & NCH_3), 2.22 (s, 3H, 8-CH_3), 2.25–2.18 (overlapped, 1H, 2a-Hβ), 1.94 ppm (s, 3H, 7′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C-4), 151.2 (C-7), 149.8 (C-9), 147.4 (C-10), 146.1 (C-3′a or 7′a), 145.6 (C-3′a or 7′a), 145.4 ($C_6H_4CH_3$), 141.1 (C-6′), 133.8 ($OCH_2CH{=}CH_2$), 133.6 ($C_6H_4CH_3$), 129.9 ($C_6H_4CH_3$), 127.8 ($C_6H_4CH_3$), 125.0 (C-8), 124.6 (C-5′), 122.4 (C-6a or 10a), 122.3 (C-6a or 10a), 117.1 ($OCH_2CH{=}CH_2$), 115.3 (C-7′), 107.5 (C-4′), 101.8 (C-2′), 72.9 ($OCH_2CH{=}CH_2$), 60.2 (9-OCH_3), 60.1 (10-OCH_3), 58.2 (C-5), 55.5 (C-2), 54.4 (C-1), 40.3 (NCH_3), 33.3 (C-2a), 24.2 (C-6), 21.7 ($C_6H_4CH_3$), 10.6 (7′-CH_3), 9.7 ppm (8-CH_3); FTIR (KBr): $\tilde{\nu}$ = 1674, 1476, 1450, 1414, 1358, 1339, 1192, 1180, 1113, 1076 cm^{-1}; MS (EI): m/z (%): 650 (18) $[M]^+$, 610 (14), 609 (38), 496 (22), 495 (38), 275 (29), 274 (100), 235 (12), 234 (39), 233 (17), 219 (11), 218 (36); HRMS (EI): m/z: calcd for $C_{34}H_{38}O_9N_2S$: 650.2298 $[M]^+$; found: 650.2294.

A solution of KOH (7.35 g, 0.111 mmol) in H_2O (33 mL) was added dropwise to a stirred solution of the above product (1.54 g) in EtOH (33 mL) at 25 °C, and the mixture was heated at reflux for 3 h. The mixture was diluted with H_2O (130 mL), neutralized with 6 M aq HCl solution, and extracted with $CHCl_3$ (3×200 mL). The combined extract was washed with brine (200 mL), dried, and concentrated in vacuo to give a residue (1.10 g), which was subjected to column chromatography on SiO_2 (30 g) with $CHCl_3$/MeOH (97:3) to afford **10** (889.1 mg, 80%, two steps) as a brown amorphous powder; R_f = 0.24 ($CHCl_3$/MeOH 97:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (s, 1H, 4′-H), 6.06 (ddt, J = 17.6, 10.6, 5.5 Hz, 1H, $OCH_2CH{=}CH_2$), 5.91 (br s, 1H, *N*H), 5.87 (d, J = 1.4 Hz, 1H, 2′-H), 5.85 (d, J = 1.4 Hz, 1H, 2′-H), 5.41 (br dd, J = 17.6, 1.4 Hz, 1H, $OCH_2CH{=}CH_2$), 5.24 (br dd, J = 10.7, 1.4 Hz, 1H, $OCH_2CH{=}CH_2$), 4.30 (ddt, J = 12.5, 5.5, 1.4 Hz, 1H, $OCH_2CH{=}CH_2$), 4.27 (ddt, J = 12.5, 5.5, 1.4 Hz, 1H, $OCH_2CH{=}CH_2$), 4.21–4.18 (overlapped, 2H, 1-H & 2-H), 3.83 (s, 3H, 10-OCH_3), 3.80 (s, 3H, 9-OCH_3), 3.55 (d, J = 7.2 Hz, 1H, 5-H), 3.20 (d, J = 14.5 Hz, 1H, 2a-Hα), 3.06 (dd, J = 17.5, 7.2 Hz, 1H, 6-Hα), 2.95 (d, J = 17.5 Hz, 1H, 6-Hβ), 2.48 (s, 3H, NCH_3), 2.21 (s, 3H, 8-CH_3), 2.10 (s, 3H, 7′-CH_3), 2.02 ppm (dd, J = 14.5, 10.4 Hz, 1H, 2a-Hβ); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C-4), 151.3 (C-7), 149.8 (C-9), 147.3 (C-10 or 6′), 147.1 (C-10 or 6′), 145.5 (C-7′a), 140.8 (C-3′a), 133.7 ($OCH_2CH{=}CH_2$), 125.0 (C-8), 122.5 (C-6a or 10a), 122.4 (C-6a or 10a), 117.3 ($OCH_2CH{=}CH_2$), 115.6 (C-5′), 107.8 (C-7′), 107.5 (C-4′), 100.8 (C-2′), 73.0 ($OCH_2CH{=}CH_2$), 60.2 (10-OCH_3), 60.1 (9-OCH_3), 58.0 (C-5), 56.0 (C-2), 54.4 (C-1), 40.3 (NCH_3), 32.4 (C-2a), 24.2 (C-6), 9.7 (8-CH_3), 9.0 ppm (7′-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3370, 2936, 1655, 1476, 1456, 1412, 1339, 1252, 1238, 1184, 1111, 1092, 1076, 1057 cm^{-1}; MS (EI): m/z (%): 497 (29), 496 (100) $[M]^+$, 456 (18), 455 (48), 275 (28), 274 (89), 260 (14), 234 (39), 233 (24), 219 (13), 218 (47); HRMS (EI): m/z: calcd for $C_{27}H_{32}N_2O_7$: 496.2210 $[M]^+$; found: 496.2211.

(1R,2S*,4R*,5S*)-7-(Allyloxy)-2-[(6-hydroxy-7-methylbenzo[d]-[1,3]dioxol-5-yl)methyl]-9,10-dimethoxy-8,11-dimethyl-1,2,3,-4,5,6-hexahydro-1,5-iminobenzo[d]azocine-4-carbo-nitrile (11)*

A suspension of Cp_2ZrHCl (31.9 mg, 0.12 mmol) in THF (0.5 mL) was added to a stirred solution of **10** (19.9 mg, 0.04 mmol) in THF (1 mL) at −20 °C, and the mixture was warmed to 0 °C over 1 h. A solution of KCN (20.8 mg, 0.32 mmol) in H_2O (640 μL) was added to the above solution, and the mixture was stirred at 25 °C for 4 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with $CHCl_3$ (3×15 mL). The combined extract was washed with brine (10 mL), dried, and concentrated in vacuo to give a residue (21.5 mg), which was subjected to column chromatography on SiO_2 (6 g) with $CHCl_3$ to give **11** (19.4 mg, 96%) as a brown amorphous powder; R_f = 0.40 (hexane/$CHCl_3$ 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (s, 1H, 4′-H), 6.09 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H, $OCH_2CH{=}CH_2$), 5.86 (d, J = 1.4 Hz, 1H, 2′-H), 5.85 (d, J = 1.4 Hz, 1H, 2′-H), 5.44 (dq, J = 17.3, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 5.28 (dq, J = 10.6, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.34 (ddt, J = 12.7, 5.4, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.29 (ddt, J = 12.7, 5.4, 1.5 Hz, 1H, $OCH_2CH{=}CH_2$), 4.08 (d, J = 2.7 Hz, 1H, 1-H), 3.97 (d, J = 1.5 Hz, 1H, 4-H), 3.82 (s, 3H, 10-OCH_3), 3.80 (s, 3H, 9-OCH_3), 3.64 (dt, J = 10.2, 2.7 Hz, 1H, 2-H), 3.28 (dd, J = 7.8, 1.5 Hz, 1H, 5-H), 3.03 (dd, J = 18.7, 7.8 Hz, 1H, 6-Hα), 2.91 (dd, J = 14.9, 2.7 Hz, 1H, 2a-Hα), 2.45 (d, J = 18.7 Hz, 1H, 6-Hβ), 2.32 (s, 3H, NCH_3), 2.21 (s, 3H, 8-CH_3), 2.08 (s, 3H, 7′-CH_3), 2.02 ppm (dd, J = 14.9, 10.2 Hz, 1H, 2a-Hβ); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6 (C-7), 150.0 (C-9), 148.2 (C-6′), 147.6 (C-10), 145.4 (C-7′a), 140.2 (C-3′a), 133.7 ($OCH_2CH{=}CH_2$), 124.5 (C-8), 123.0 (C-6a), 122.0 (C-10a), 119.0 (CN), 117.3 ($OCH_2CH{=}CH_2$), 115.8 (C-5′), 108.8 (C-7′), 107.2 (C-4′), 100.7 (C-2′), 72.9 ($OCH_2CH{=}CH_2$), 60.4 (10-OCH_3), 60.2 (9-OCH_3), 57.7 (C-2), 56.6 (C-1), 53.9 (C-5), 53.5 (C-4), 42.0 (NCH_3), 34.2 (C-2a), 21.3 (C-6), 9.7 (8-CH_3), 9.1 ppm (7′-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3447, 2936, 2361, 1458, 1412, 1250, 1111, 1092, 1074, 1055, 1042, 1020 cm^{-1}; MS (FAB): m/z (%): 508 $[M{+}H]^+$; HRMS (FAB): m/z: calcd for $C_{28}H_{34}N_3O_6$: 508.2448 $[M]^+$; found: 508.2452.

***(1R*,2S*,5S*)*-tert-*Butyl 7-(allyloxy)-2-{(6′-[(tert-butoxycarbonyl)oxy-7′-methylbenzo-[d][1,3]dioxol-5-yl]methyl}-9,10-dimethoxy-8,11-dimethyl-4-oxo-1,2,5,6-tetrahydro-1,5-iminobenzo[d]azocine-3(4H)-carboxylate (13)**

A mixture of **10** (568.5 mg, 1.14 mmol) and DMAP (279.4 mg, 2.29 mmol, 2 equiv) in MeCN (11.5 mL) was cooled at 0 °C; then, Boc_2O (5.3 mL, 22.90 mmol, 20 equiv.) was added to the mixture, which was heated at reflux for 17.5 h. As the starting material still remained, as indicated by TLC monitoring, DMAP (279.4 mg, 2.29 mmol, 2 equiv.) was added to the mixture at 25 °C, and the reaction mixture was heated under reflux for an additional 40 h. The mixture was diluted with H_2O (30 mL) and extracted with $CHCl_3$ (3×50 mL). The combined extract was washed with brine (50 mL), dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (15 g) with hexane/EtOAc (11:9) to afford **13** (570.9 mg, 72%) as a brown amorphous powder; R_f = 0.30 (hexane/EtOAc 11:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (s, 1H, 4′-H), 6.07 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H, CH_2CH=CH_2), 5.90 (s, 2H, 2′-H_2), 5.42 (dq, J = 17.3, 1.5 Hz, 1H, CH_2CH=CH_2), 5.26 (dq, J = 10.6, 1.5 Hz, 1H, CH_2CH=CH_2), 4.99 (q, J = 6.2 Hz, 1H, 2-H), 4.39 (dd, J = 6.2, 1.5 Hz, 1H, 1-H), 4.32 (ddt, J = 12.4, 5.4, 1.5 Hz, 1H, CH_2CH=CH_2), 4.26 (ddt, J = 12.4, 5.4, 1.5 Hz, 1H, CH_2CH=CH_2), 3.77 (dd, J = 7.7, 1.5 Hz, 1H, 5-H), 3.72 (s, 3H, 9-OCH_3), 3.61 (s, 3H, 10-OCH_3), 3.07 (dd, J = 18.5, 7.7 Hz, 1H, 6H-α), 2.96 (dd, J = 18.5, 1.5 Hz, 1H, 6-Hβ), 2.91 (dd, J = 15.6, 6.2 Hz, 1H, 2a-Hα), 2.46 (s, 3H, NCH_3), 2.18 (s, 3H, 8-CH_3), 2.05 (s, 3H, 7′-CH_3), 1.99 (dd, J = 15.6, 6.2 Hz, 1H, 2a-Hβ), 1.49 (s, 9H, $C(CH_3)_3$), 1.31 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (C-4), 151.6 (CO_2), 151.5 (CO_2), 151.1 (C-7), 149.8 (C-9), 147.6 (C-10), 144.7 (C-7′a), 144.3 (C-3′a), 142.6 (C-6′), 133.7 (CH_2CH=CH_2), 125.1 (C-8), 124.0 (C-5′), 122.9 (C-10a), 121.8 (C-6a), 117.3 (CH_2CH=CH_2), 112.9 (C-7′), 105.7 (C-4′), 101.2 (C-2′), 83.5 ($C(CH_3)_3$), 82.9 ($C(CH_3)_3$), 73.1 (CH_2CH=CH_2), 60.1 (10-OCH_3), 59.8 (9-OCH_3), 59.8 (C-5), 57.8 (C-2), 54.0 (C-1), 40.0 (NCH_3), 32.3 (C-2a), 27.6 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$), 22.7 (C-6), 9.6 (8-CH_3), 9.4 ppm (7′-CH_3); FTIR (KBr): $\tilde{\nu}$ = 1757, 1732, 1697, 1477, 1456, 1412, 1395, 1369, 1341, 1275, 1256, 1152, 1099, 1063 cm^{-1}; MS (EI): *m/z* (%): 696 (4) $[M]^+$, 596 (13), 555 (13), 497 (14), 496 (47), 455 (24), 275 (31), 274 (100), 271 (14), 260 (11), 234 (32), 233 (22), 232 (12), 219 (11), 218 (38), 57 (14); HRMS (EI): *m/z*: calcd $C_{37}H_{48}N_2O_{11}$: 696.3258 $[M]^+$; found: 696.3256.

***6-(2′S*)-(1″R,3″S)-[(5″-Allyloxy-3″-hydroxymethyl-7″, 8″-dimethoxy-2″,6″-dimethyl-1″,2″,3″,4″-tetrahydroisoquinolin-1″-yl)-2′-aminoethyl]-4-methylbenzo[d][1,3]dioxol-5-ol (14)**

$NaBH_4$ (892.4 g, 23.59 mmol) was added to a stirred solution of **13** (821.8 mg, 1.179 mmol) in EtOH (12 mL) at 0 °C, and the mixture was stirred at 25 °C for 3 h. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and H_2O (40 mL) at 0 °C and extracted with $CHCl_3$ (3×50 mL). The combined extract was washed with brine (30 mL), dried, and concentrated in vacuo to give a residue, which was used in the next step without further purification. An analytical sample of the protected compound (857.3 mg) was obtained as a colorless amorphous powder by column chromatography with hexane/EtOAc (13:7); R_f = 0.21 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1H, 4″-H), 6.05 (ddt, J = 17.1, 10.8, 5.6 Hz, 1H, CH_2CH=CH_2), 5.90 (d, J = 1.4 Hz, 1H, 2″-H), 5.88 (d, J = 1.4 Hz, 1H, 2″-H), 5.38 (dd, J = 17.1, 1.4 Hz, 1H, CH_2CH=CH_2), 5.22 (dd, J = 10.8, 1.4 Hz, 1H, CH_2CH=CH_2), 4.49 (brd, J = 9.5 Hz, 1H, 1-H), 4.27 (dd, J = 12.5, 5.6 Hz, 1H, CH_2CH=CH_2), 4.12 (dd, J = 12.5, 5.6 Hz, 1H, CH_2CH=CH_2), 3.88–3.76 (overlapped, 1H, 2-H), 3.86 (s, 3H, 8′-OCH_3), 3.83 (s, 3H, 7′-OCH_3), 3.77 (d, J = 9.5 Hz, 1H, 1′-H), 3.48 (dd, J = 11.3, 3.3 Hz, 1H, 2-H), 3.13 (brd, J = 13.1 Hz, 1H, 3′a-H), 2.88 (dd, J = 15.5, 4.8 Hz, 1H, 4′-H), 2.75 (dd, J = 15.5, 12.6 Hz, 1H, 4′-H), 2.50 (s, 3H, NCH_3), 2.38 (m, 1H, 3′- and 3′a-H), 2.17 (s, 3H; 6′-CH_3), 2.06 (s, 3H, 7″-CH_3), 1.57 (s, 9H, $C(CH_3)_3$), 1.14 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (*C*O), 151.9 (*C*O), 150.0 (C-5′), 149.0 (C-7′), 146.5 (C-8′), 145.0 (C-7″a), 144.6 (C-3″a), 142.4 (C-6″), 133.9 (CH_2CH=CH_2), 126.7 (C-4′a or 8′a), 125.9 (C-4′a or 8′a), 124.0 (C-6′ or 5″), 123.8 (C-6′ or 5″), 117.4 (CH_2CH=CH_2), 112.9 (C-7″), 106.8 (C-4″), 101.2 (C-2″), 83.5 ($C(CH_3)_3$), 78.3 ($C(CH_3)_3$), 74.1 (CH_2CH=CH_2), 64.4 (C-2), 63.7 (C-1′), 63.1 (C-3′), 60.5 (8′-OCH_3), 60.1 (7′-OCH_3), 55.6 (C-1), 46.6 (NCH_3), 32.6 (C-3′a), 28.1 ($C(CH_3)_3$), 27.6 ($C(CH_3)_3$), 24.4 (C-4′), 9.50 (6′-CH_3), 9.45 ppm (7″-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3422, 2978, 2930, 1751, 1715, 1516, 1477, 1458, 1369, 1281, 1258, 1153, 1101, 1063 cm^{-1}; MS (FAB): *m/z* (%): 701 $[M+H]^+$; HRMS (FAB): *m/z*: calcd for $C_{37}H_{53}N_2O_{11}$: 701.3649 $[M]^+$; found: 701.3646.

TFA (18 mL) was added to a stirred solution of the crude product in CH_2Cl_2 (36 mL) at 0 °C, and the mixture was stirred at 25 °C for 1.5 h. The mixture was diluted with H_2O (40 mL) at 0 °C, made alkaline with concentrated NH_4OH (30 mL), and extracted with $CHCl_3$ (3×80 mL). The combined extract was washed with brine (60 mL), dried, and concentrated in vacuo to give a residue (568.6 mg), which was subjected to column chromatography on SiO_2 (15 g) with $CHCl_3$/MeOH (97:3) to afford **14** (433.2 mg, 73%, two steps) as a brown amorphous powder; R_f = 0.19 ($CHCl_3$/MeOH 97:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 1H, 7-H), 6.05 (ddt, J = 17.0, 10.4, 5.6 Hz, 1H, CH_2CH=CH_2), 5.87 (d, J = 1.4 Hz, 1H, 2-H), 5.82 (d, J = 1.4 Hz, 1H, 2-H), 5.37 (dq, J = 17.0, 1.4 Hz, 1H, CH_2CH=CH_2), 5.25 (dq, J = 10.4, 1.4 Hz, 1H, CH_2CH=CH_2), 4.25 (ddt, J = 11.1, 5.6, 1.4 Hz, 1H, CH_2CH=CH_2), 4.19 (ddt, J = 11.1, 5.6, 1.4 Hz, 1H, CH_2CH=CH_2), 3.84 (s, 3H, 8″-OCH_3), 3.80 (s, 3H, 7″-OCH_3), 3.79 (dd, J = 10.5, 4.0 Hz, 1H, 3″a-H), 3.67 (d, J = 9.4 Hz, 1H, 1″-H), 3.46 (dd, J = 10.5, 2.6 Hz, 1H, 3′a-H), 3.14 (d, J = 13.6 Hz, 1H, 1′-H), 2.95 (d, J = 11.0 Hz, 1H, 4″-H), 2.75 (dd, J = 13.6, 9.4 Hz, 1H, 1′-H), 2.69 (t, J = 9.4 Hz, 1H, 2′-H), 2.51 (s, 3H, NCH_3), 2.42–2.32 (overlapped, 2H, 3″- & 4″-H), 2.21 (s, 3H, 6″-CH_3), 2.11 ppm (s, 3H, 4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6 (C-5 or 5″), 150.4 (C-5 or 5″), 149.7 (C-7″), 146.9 (C-8″), 145.4 (C-3a), 139.3 (C-7a), 133.5 (CH_2CH=CH_2), 126.7 (C-8″a), 124.8 (C-4″a or 6″), 124.6 (C-4″a or 6″), 117.7 (CH_2CH=CH_2), 117.6 (C-6), 109.3 (C-4), 107.0 (C-7), 100.5 (C-2), 74.5 (CH_2CH=CH_2), 65.0 (C-1″), 63.9 (C-3″a), 63.0 (C-3″), 60.7 (8″-OCH_3), 60.1 (7″-OCH_3), 59.1 (C-2′), 46.6 (NCH_3), 38.2 (C-1′), 24.3 (C-4″), 9.7 (6″-CH_3), 9.3 ppm (4-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3441, 3370, 2938, 2866, 1470, 1414, 1248, 1115, 1094, 1057, 934 cm^{-1}; MS (EI): *m/z* (%): 500 (1) $[M]^+$, 307 (18), 306 (100), 234 (15), 218 (10); HRMS (EI): *m/z*: calcd $C_{27}H_{36}N_2O_7$: 500.2523 $[M]^+$; found: 500.2520.

***(6aS*,7R*,13S*,14R*,16R*)-Ethyl 5-(benzyloxy)-14-cyano-11-hydroxy-8,9-dimethoxy-4,10,17-trimethyl-6a,7,12,13,14,16-hexahydro-6H-7,13-iminobenzo[4,5]azocino-[1,2-b]-[1,3]-dioxolo[4,5-h]isoquinoline-16-carboxylate (18)**

14→**15**: A solution of 1-allyl 3-ethyl 2,2-dihydroxymalonate[20] (238.2 mg, 1.167 mmol) in TFA (6 mL) was added to a stirred solution of **14** (116.8 mg, 0.233 mmol) in AcOH (1.5 mL), and the mixture was stirred at 25 °C for 6 h. The mixture was diluted with H_2O (60 mL) at 0 °C, made alkaline with concentrated NH_4OH (11 mL), and extracted with $CHCl_3$ (3×80 mL). The combined extract was washed with brine (40 mL), dried, and concentrated in vacuo to give a residue (358.9 mg), which was subjected to column chromatography on SiO_2 (10 g) with hexane/EtOAc (2:3) to afford an inseparable 1:1 diastereomer mixture of **15** (124.9 mg, 80%) as a yellow amorphous powder.

15→**16**: BnBr (533 μL, 4.40 mmol) was added to a stirred solution of **15** (147.1 mg, 0.22 mmol) in the presence of K_2CO_3 (763.9 mg, 5.50 mmol) in acetone (55 mL), and the mixture was stirred at 25 °C for 8 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (6 g) with hexane/EtOAc (1:1) to afford an inseparable 1:1 diastereomer mixture of **16** (137.2 mg, 83 %) as a yellow amorphous powder.

16→**17**: $(COCl)_2$ (25 μL, 0.3 mmol) was added to a stirred solution of DMSO (43 μL, 0.6 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the mixture was stirred at −78 °C for 15 min. A solution of **16** (45.5 mg, 60 μmol) in CH_2Cl_2 (1 mL) was added to the above solution at −78 °C over 10 min, and the mixture was stirred at −78 °C for 4 h. Et_3N (167 μL, 1.2 mmol) was then added to the mixture at −78 °C over 5 min, and stirring was continued at −78 °C for 30 min. After the mixture was warmed to 25 °C over a period of 3 h and stirred for 2 h, it was diluted with saturated aqueous $NaHCO_3$ solution (5 mL) at 0 °C and extracted with $CHCl_3$ (3×10 mL). The combined extract was washed with brine (10 mL), dried, and concentrated in vacuo to give a residue that was used in the next step without purification. A solution of KCN (31.9 mg, 0.48 mmol) in H_2O (960 μL) was added to a stirred solution of the crude product (63.4 mg) in THF (1 mL) in the presence of AcOH (381 μL, 6.6 mmol) at 0 °C, and the mixture was stirred at 25 °C for 2 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and extracted with $CHCl_3$ (3×10 mL). The combined extract was washed with brine (10 mL), dried, and concentrated in vacuo to give a residue (41.5 mg), which was subjected to column chromatography on SiO_2 (6 g) with hexane/EtOAc (3:1) to afford an inseparable 1:1 diastereomer mixture of **17** (25.8 mg, 56 %, two steps) as a colorless amorphous powder.

17→**18**: A solution of $Pd(PPh_3)_4$ (16.4 mg, 13.8 μmol) in THF (1.0 mL) was added to a stirred solution of **17** (35.2 mg, 46 μmol) and dimedone (32.6 mg, 0.23 mmol) in THF (2.0 mL) under an argon atmosphere, and the mixture was stirred at 25 °C for 1 h. After the mixture was concentrated in vacuo, the resulting residue was dissolved in $CHCl_3$ (2.5 mL) and heated at reflux for 2 h. The mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (6 g) with $CHCl_3$/EtOAc (4:1) to afford **18** (21.2 mg, 72 %, two steps) as a pale-yellow amorphous powder; R_f = 0.20 ($CHCl_3$/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (m, 2H, C_6H_5), 7.46 (m, 2H, C_6H_5), 7.40 (m, 1H, C_6H_5), 5.94 (d, J = 1.4 Hz, 1H, 2-H), 5.89 (d, J = 1.4 Hz, 1H, 2-H), 4.70 (d, J = 10.4 Hz, 1H, $PhCH_2$), 4.58 (d, J = 10.4 Hz, 1H, $PhCH_2$), 4.47 (s, 1H, 16-H), 4.39 (brs, 1H, *O*H), 4.27 (d, J = 2.5 Hz, 1H, 14-H), 4.07 (dq, J = 10.9, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 4.04 (brd, J = 2.6 Hz, 1H, 7-H), 3.95 (dq, J = 10.9, 7.1 Hz, 1H, C*H*$_2$CH$_3$), 3.77 (s, 3H, 8-OCH_3), 3.72 (s, 3H, 9-OCH_3), 3.43 (brd, J = 8.1 Hz, 1H, 13-H), 3.30 (dd, J = 15.4, 2.6 Hz, 1H, 6H-α), 3.20 (dt, J = 11.7, 2.6 Hz, 1H, 6a-H), 2.91 (dd, J = 17.6, 8.1 Hz, 1H, 12-Hα), 2.33 (d, J = 17.6 Hz, 1H, 12-Hβ), 2.32 (s, 3H, *N*CH_3), 2.17 (s, 3H, 4-CH_3), 2.13 (s, 3H, 10-CH_3), 2.02 (dd, J = 15.4, 11.7 Hz, 1H, 6-Hβ), 1.04 ppm (t, J = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (*C*O), 149.0 (C-9), 148.2 (C-5), 146.5 (C-11), 144.9 (C-8), 144.4 (C-3a), 140.0 (C-16b), 137.1 (C_6H_5), 128.6 (C_6H_5), 128.5 (C_6H_5), 128.3 (C_6H_5), 123.0 (C-7a), 121.1 (C-5a or 16a), 117.6 (CN), 116.1 (C-11a), 115.6 (C-10), 113.1 (C-4), 109.9 (C-5a or 16a), 101.4 (C-2), 75.3 ($PhCH_2$), 61.3 (*C*H$_2$CH$_3$), 61.1 (C-14), 60.3 (C-16, 8 & 9-OCH_3), 56.8 (C-6a & 7), 54.9 (C-13), 41.8 (*N*CH_3), 26.3 (C-6), 21.0 (C-12), 13.7 (CH$_2$*C*H$_3$), 9.4 (4-CH_3), 8.6 ppm (10-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3437, 2934, 2228, 1728, 1456, 1431, 1416, 1344, 1254, 1109, 1092, 1074, 1028 cm^{-1}; MS (EI): *m/z* (%): 641 (7) $[M]^+$, 543 (14), 541 (17), 523 (19), 451 (23), 450 (18), 274 (40), 235 (33), 234 (100); HRMS (EI): *m/z*: calcd for $C_{36}H_{39}N_3O_8$: 641.2737 $[M]^+$; found: 641.2735.

(6aS,7R*,13S*,14R*,16R*)-5-(Benzyloxy)-11-hydroxy-16-(hydroxymethyl)-8,9-dimethoxy-4,10,17-trimethyl-6a,7,12,-13,14,16-hexahydro-6H-7,13-iminobenzo[4,5]azocino-[1,2-b]-[1,3]-dioxolo[4,5-h]isoquinoline-14-carbonitrile (19)*

$LiBH_4$ (6.4 mg, 0.281 mmol) was added to a stirred solution of **18** (18.0 mg, 28.1 μmol) in THF (1 mL) and MeOH (11 μL, 0.281 mmol), and the mixture was stirred at 25 °C for 3 h. After the mixture was diluted with brine (5 mL) slowly at 0 °C, it was extracted with $CHCl_3$ (2×10 mL) and then $CHCl_3$/MeOH (19:1, 2×10 mL). The combined extract was dried and concentrated in vacuo to give a residue (19.6 mg), which was subjected to column chromatography on SiO_2 (6 g) with $CHCl_3$/EtOAc (3:2) to afford **19** (11.9 mg, 71 %) as a colorless amorphous powder; R_f = 0.24 (hexane/EtOAc 2:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (m, 2H, C_6H_5), 7.46 (m, 2H, C_6H_5), 7.40 (m, 1H, C_6H_5), 5.95 (d, J = 1.4 Hz, 1H, 2-H), 5.89 (d, J = 1.4 Hz, 1H, 2-H), 4.67 (d, J = 10.4 Hz, 1H, $PhCH_2$), 4.58 (brs, 1H, *O*H), 4.55 (d, J = 10.4 Hz, 1H, $PhCH_2$), 4.08 (d, J = 2.3 Hz, 1H, 14-H), 4.07 (d, J = 2.5 Hz, 1H, 7-H), 4.01 (t, J = 3.3 Hz, 1H, 16-H), 3.77 (s, 3H, 8-OCH_3), 3.70 (s, 3H, 9-OCH_3), 3.68 (brd, J = 11.3 Hz, 1H, C*H*$_2$OH), 3.50 (dd, J = 11.3, 3.3 Hz, 1H, C*H*$_2$OH), 3.47 (brd, J = 9.0 Hz, 1H, 13-H), 3.31 (dt, J = 12.8, 2.5 Hz, 1H, 6a-H), 3.31 (dd, J = 16.0, 2.5 Hz, 1H, 6H-α), 2.99 (dd, J = 18.1, 9.0 Hz, 1H, 12-Hα), 2.40 (d, J = 18.1 Hz, 1H, 12-Hβ), 2.36 (s, 3H, *N*CH_3), 2.16 (s, 3H, 4-CH_3), 2.14 (s, 3H, 10-CH_3), 1.93 ppm (dd, J = 16.0, 12.8 Hz, 1H, 6-Hβ); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3 (C-9), 148.2 (C-5), 146.7 (C-11), 145.0 (C-8), 144.5 (C-3a), 139.1 (C-16b), 137.1 (C_6H_5), 128.6 (C_6H_5), 128.4 (C_6H_5), 128.3 (C_6H_5), 123.2 (C-7a), 121.1 (C-5a), 117.7 (CN), 116.0 (C-10), 115.6 (C-11a), 113.4 (C-16a), 112.5 (C-4), 101.2 (C-2), 75.1 ($PhCH_2$), 63.4 (*C*H$_2$OH), 60.3 (8 & 9-OCH_3), 60.0 (C-14), 58.1 (C-16), 56.9 (C-7), 56.5 (C-6a), 54.9 (C-13), 41.8 (*N*CH_3), 26.3 (C-6), 21.3 (C-12), 9.3 (4-CH_3), 8.7 ppm (10-CH_3); FTIR (KBr): $\tilde{\nu}$ = 3447, 2934, 2228, 1456, 1431, 1418, 1344, 1109, 1092, 1074 cm^{-1}; MS (EI): *m/z* (%): 599 (1) $[M]^+$, 572 (17), 544 (17), 543 (47), 338 (41), 264 (18), 248 (10), 236 (18), 235 (28), 234 (100), 218 (10), 91 (10); HRMS (EI): *m/z*: calcd for $C_{34}H_{37}N_3O_7$: 599.2632 $[M]^+$; found: 599.2629.

(6aS,7R*,13S*,14R*,16R*)-5-(Benzyloxy)-16-(hydroxymethyl)-9-methoxy-4,10,17-trimethyl-8,11-dioxo-6a,7,8,11,12,13,14,16-octahydro-6H-7,13-iminobenzo[4,5]azocino[1,2-b][1,3]-dioxolo[4,5-h]isoquinoline-14-carbonitrile (20)*

A solution of CAN (21.6 mg, 37.5 μmol) in H_2O (700 μL) was added to a stirred solution of **19** (9.00 mg, 15 μmol) in THF (2.1 mL) at 0 °C, and the mixture was stirred at 0 °C for 20 min. The mixture was diluted with H_2O (5 mL) and then extracted with EtOAc (3×10 mL). The combined extract was washed with brine (5 mL), dried, and concentrated in vacuo to give a residue (9.8 mg), which was subjected to column chromatography on SiO_2 (6 g) with hexane/EtOAc (1:1) to afford **20** (4.43 mg, 51 %) as a yellow gummy solid. Compound **20** was identical with an authentic sample[13a] on direct comparison of the characterization data (^{1}H NMR, ^{13}C NMR, IR, MS) and TLC behavior; R_f = 0.20 (hexane/EtOAc 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.36 (m, 5H, C_6H_5), 5.98 (d, J = 1.4 Hz, 1H, 2-H), 5.90 (d, J = 1.4 Hz, 1H, 2-H), 4.66 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.60 (d, J = 10.6 Hz, 1H, $PhCH_2$), 4.15 (d, J = 2.5 Hz, 1H, 14-H), 4.04 (t, J = 4.3 Hz, 1H, 16-H), 4.01 (brd, J = 2.7 Hz, 1H, 7-H), 3.94 (s, 3H, 9-OCH_3), 3.71 (brd, J = 10.8 Hz, 1H, C*H*$_2$OH), 3.51(m, 1H, C*H*$_2$OH), 3.39 (brd, J = 7.6 Hz, 1H, 13-H), 3.18 (dt, J = 12.1, 2.7 Hz, 1H, 6a-H), 3.04

(dd, $J=15.1$, 2.7 Hz, 1H, 6H-α), 2.82 (dd, $J=20.8$, 7.6 Hz, 1H, 12-Hα), 2.30 (s, 3H, NCH_3), 2.29 (d, $J=20.8$ Hz, 1H, 12-Hβ), 2.16 (s, 3H, 4-CH_3), 1.95 (s, 3H, 10-CH_3), 1.66 ppm (dd, $J=15.1$, 12.1 Hz, 1H, 6-Hβ); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=186.5$ (C-11), 182.5 (C-8), 155.3 (C-9), 148.2 (C-5), 144.9 (C-3a), 141.3 (C-11a), 139.2 (C-16b), 136.7 (C_6H_5), 136.2 (C-7a), 128.6 (C_6H_5), 128.6 (C-10), 128.5 (C_6H_5), 128.3 (C_6H_5), 120.6 (C-5a), 117.4 (CN), 112.6 (C-4 & 16a), 101.3 (C-2), 75.5 ($PhCH_2$), 65.2 (CH_2OH), 60.9 (9-OCH_3), 59.8 (C-14), 58.5 (C-16), 56.0 (C-6a), 54.8 (C-7 or 13), 54.7 (C-7 or 13), 41.5 (NCH_3), 27.7 (C-6), 21.5 (C-12), 9.4 (4-CH_3), 8.7 ppm (10-CH_3); FTIR (KBr): $\tilde{\nu}=2936$, 1653, 1614, 1456, 1429, 1306, 1105, 1092 cm^{-1}; MS (FAB): *m/z* (%): 583 $[M+H]^+$; HRMS (FAB): *m/z*: calcd for $C_{33}H_{33}N_3O_7$: 583.2319 $[M]^+$; found: 584.2391.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cyclization · decarboxylation · fused-ring systems · natural products · total synthesis

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[22] We found that sodium *p*-toluenesulfinate was the most effective additive, as it exclusively afforded the desired product in the total synthesis of saframycin A (**3**). However, whereas the transformation of **17** into **18** in the presence of sodium *p*-toluenesulfinate led to removal of the allyl group in the diester at C1 and to the decarboxylation of **17**, the allyl group in the E ring could not be removed. Finally, we found that sodium *p*-toluenesulfinate and dimedone were used in the removal of allyl groups and the decarboxylation sequence of **17**, and desired ethyl ester **18** was obtained in 67% overall yield in a one-pot process.
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