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SPECIAL FEATURE: ARTICLE

Synthesis of the ABCDG ring skeleton of communesin F based on carboborylation of 1,3-diene and $Bi(OTf)_3$-catalyzed cyclizations

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Abstract

Communesins, isolated from the mycelium of a strain of *Penicillium* sp., are cytotoxic heptacyclic indole alkaloids bearing a bis-aminal structure and two contiguous quaternary carbon centers. Toward a total synthesis of communesin F, we synthesized a pentacyclic ABCDG ring skeleton via carboborylation of 1,3-diene and a Friedel–Crafts-type cyclization, resulting in the formation of an azepine ring through a $Bi(OTf)_3$-catalyzed S_N2' reaction.

Introduction

Communesins A and B, which were originally isolated by Numata et al. from the mycelium of a strain of *Penicillium* sp. attached to the marine alga *Enteromorpha intestinalis*, are heptacyclic indole alkaloids (Fig. 1) [1]. Spectroscopic analyses, including nuclear magnetic resonance (NMR) spectroscopy (^{1}H NMR, ^{13}C NMR including 2D NMR) and high-resolution mass spectrometry, have revealed that their structures are quite unique. They are characterized by a heptacyclic skeleton bearing two aminals and two contiguous quaternary carbon centers. To date, nine congeners have been reported [2–6], and perophoramidine is also known as a structurally related bis-amidine indole alkaloid [7]. Recently, Tang et al. confirmed that communesins can be biosynthetically produced through the coupling of aurantioclavine and tryptamine based on genetic inactivation studies [8]. Communesins show cytotoxicity against P388 lymphocytic leukemia cells (ED_{50} A: 3.5 μg/mL, B: 0.45 μg/mL) and potent insecticidal activity toward silkworms (LD_{50} D: 300 μg/g, E: 80 μg/g). Because of their unique structure and biological activity, many research groups have conducted synthetic studies of communesins, in which various synthetic methods were developed [9–14]. The first racemic total synthesis of communesin F was achieved by Qin et al. based on an intramolecular cyclopropanation strategy [15]. Weinreb and Funk also reported total synthesis of communesin F, independently [16, 17]. The first asymmetric total syntheses of communesins A, B, and F were accomplished by Ma et al. [18, 19]. Asymmetric total syntheses were also reported by Stoltz, Movassaghi, Yang, and Chen, independently [20–23]. We have also engaged in the development of synthetic strategies for this class of alkaloids, including communesins, perophoramidine, and aurantioclavin [24–31].

Dedication: Dedicated to Professor SJ Danishefsky and his great contribution to total synthesis of highly complex and biologically important natural products.

Supplementary information The online version of this article (https://doi.org/10.1038/s41429-019-0142-7) contains supplementary material, which is available to authorized users.

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Results and discussion

Recently, we have developed palladium(Pd)-catalyzed carbosilylation of 1,3-diene with carbamoyl chloride for the synthesis of several spirooxindoles [32]. Extending this reaction, a Pd-catalyzed carboborylation of 1,3-diene was developed for a synthesis of iminoindoline [30]. Considering our developed method, it was envisioned that communesin F would be accessed from a pentacyclic skeleton **II** through intermediate **I** by the introduction of an aminoethyl unit and the formation of amidine. The pentacyclic skeleton **II** would be constructed from a tetracyclic compound **IV** via **III** by

the introduction of an allyl alcohol unit, resulting in an S_N2' reaction for the formation of an azepine ring and a reduction of amidine. The tetracyclic compound **IV** can be synthesized by a carboborylation of 1,3-diene **VI** and an intramolecular Friedel–Crafts-type reaction of a resultant iminoindoline **V** [30]. Following this retrosynthetic analysis, we have recently succeeded in the construction of tetracyclic skeleton **IV** (R = OMe) from diene **VI** (R = OMe) through iminoindoline **V** (R = OMe). However, compound **1** could not be converted to compound **2** through removal of the methyl group, although we tried various conditions, including BBr_3, BCl_3, $AlCl_3$, LiCl, Ph_2PLi, and pMeC$_6$H$_4$SLi (Scheme 1b, also see Supplementary Information, Figure S1). These reaction conditions resulted in the removal of a Cbz group or the decomposition of compound **1**. Therefore, we needed to revise our initial synthetic route and planned to employ a 1,3-diene-containing triflate (R = OTf) to avoid a protecting group manipulation. The use of a substrate bearing a triflate group for Pd-catalyzed carboborylation would extend its reaction scope, and it might react itself under the reaction conditions. In this paper, we report the construction of a pentacyclic skeleton of communesin F by extending our strategy based on carboborylation of 1,3-diene.

The synthesis started with a removal of a methyl group on a phenolic hydroxy group. A methoxy aniline derivative **3**, which was prepared from *tert*-butyl(3-methoxyphenyl) carbamate in four steps [30], was treated with BBr_3 to give a phenol (Scheme 2). The resultant phenolic hydroxy group was silylated with *tert*-butyldimethylsilyl (TBS) chloride and imidazole to give compound **4**. A half reduction of a lactone with diisobutylaluminum hydride (DIBAL-H) was followed by Wittig olefination, which gave diene **5** through internal transfer of a TBS group. After the formation of urea by a treatment with phenyl isocyanate, a phenolic hydroxy group was protected as a triflate. A removal of a TBS group was followed by a Mitsunobu reaction with *p*NsNHBoc [33] to give compound **8**, which was converted to carbodiimide **9** through dehydration with CBr_4, PPh_3, and Et_3N. Because compound **9** was unstable, it was necessary to use it immediately for the next reaction.

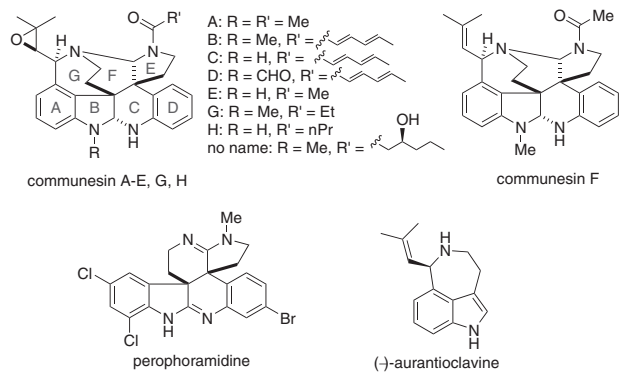
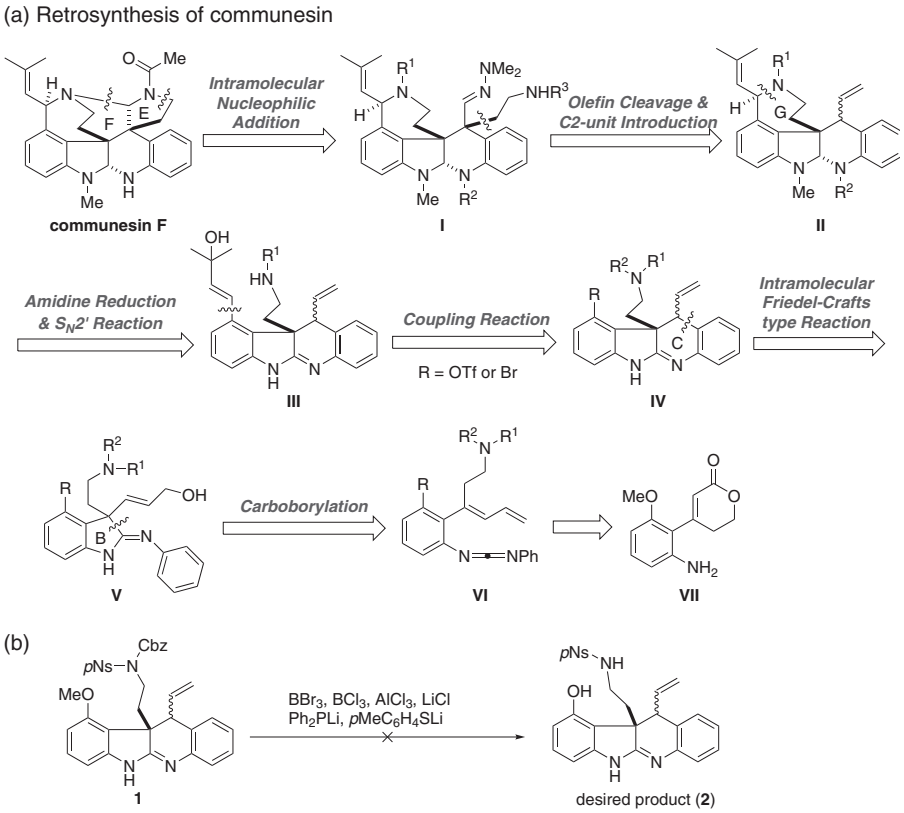
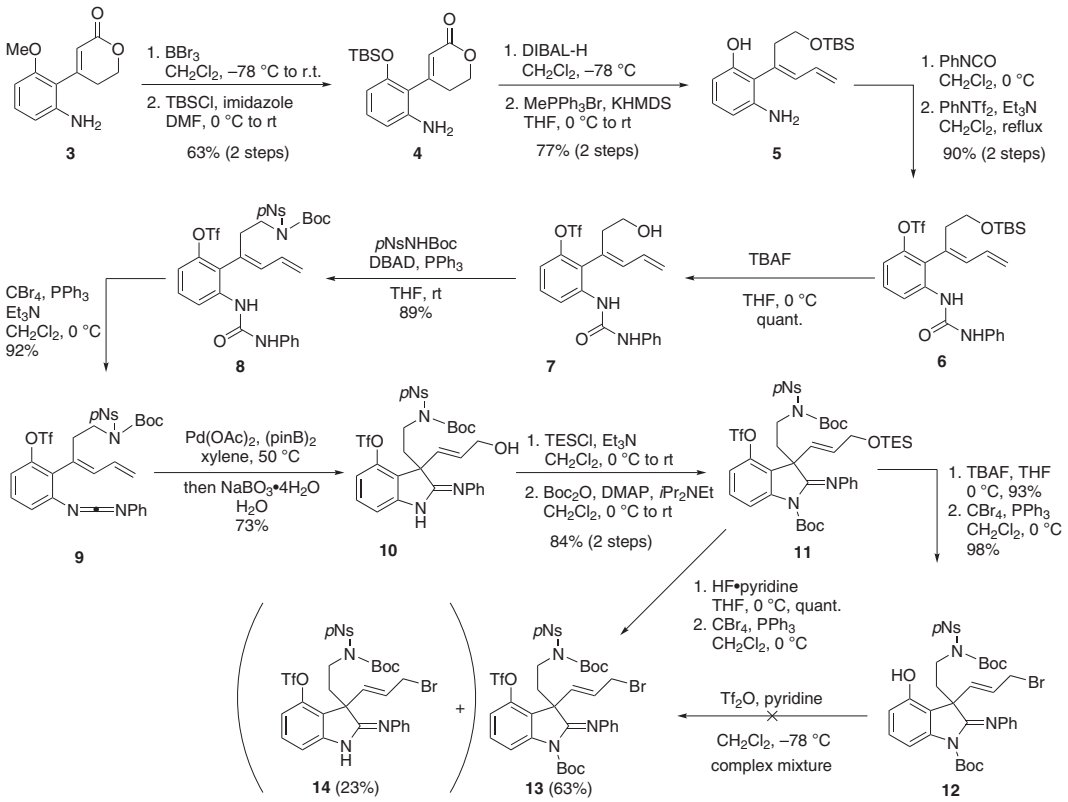


Fig. 1 Communesins and related alkaloids

Scheme 1 **a** Retrosynthesis of communesin F and **b** failed attempt at removing a methyl group from compound **1**





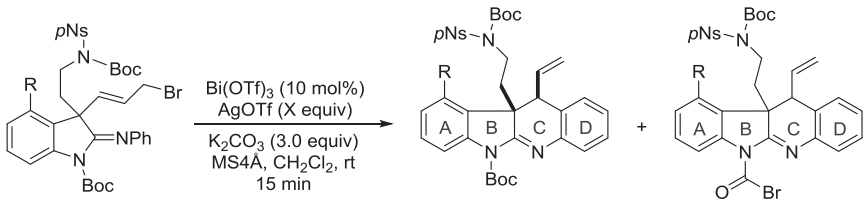
Scheme 2 Synthesis of 3,3-disubstituted iminoindoline **10** based on the Pd-catalyzed carboborylation of 1,3-diene and its derivatization

With carbodiimide **9** containing a diene moiety, we investigated whether the triflate is intact under the reaction conditions of Pd-catalyzed carboborylation of 1,3-diene. In the previous literature, there is no report concerning Pd(II)-catalyzed Miyaura borylation of triflates and diborone without a ligand, but reactions using diphenylphosphinoferrocene [34] or the reaction of arylbromide have been reported [35]. Therefore, it was expected that a triflate group would be intact during the carboborylation of 1,3-diene. As expected, the reaction of **9** proceeded smoothly under the established conditions ($Pd(OAc)_2$, $(pinB)_2$, xylene, 50 °C) to give an allyl borane, which was treated with $NaBO_3{\cdot}4H_2O$ to give allyl alcohol **10**. After silylation of allyl alcohol **10**, a *tert*-butoxycarbonyl (Boc) group was introduced to an amidine nitrogen for further transformation. The treatment of compound **11** with tetrabutylammonium fluoride gave an allyl alcohol along with the removal of the trifluoromethanesulfonyl (Tf) group, which was converted to allyl bromide **12** under standard conditions. Unfortunately, the resultant allyl bromide **12** could not be converted to compound **13** through a treatment with Tf_2O and pyridine. On the other hand, when HF·pyridine was used, a triethylsilyl group was selectively removed with the triflate group intact. The resultant allyl alcohol was also converted to allyl bromide **13** containing a triflate group, while a small amount of compound **14** was also obtained through the removal of a Boc group.

Next, we investigated Friedel–Crafts-type cyclization of allyl bromides **12** and **13** to construct a tetracyclic ABCD ring skeleton. Previously, we have reported the cyclization of compound **15** containing a methoxy group using 10 mol % of $Bi(OTf)_3$ and 3.5 equivalents of AgOTf (Table 1, entry 1) [30, 36–38]. The reaction gave compound **18a** in 49% yield along with **18b** in 30% yield. We initially applied these conditions to a cyclization of compound **13** containing a triflate group. However, the reaction gave a complex mixture instead of any cyclized products **17a** and **17b** (entry 2). On the other hand, the cyclization of compound **12** containing a phenolic hydroxy group proceeded under the same conditions to give compounds **16a** and **16b** in 63 and 30% yields with excellent stereochemistry, respectively (entry 3). The stereochemistry was determined by a comparison with our previous results [30] and a NOESY experiment of a derivatized compound **28** (*vide infra*). When 3.5 equivalents of AgOTf was reduced to 1.2 equivalents, the formation of byproduct **16b** was suppressed to 17% yield (entry 4). Finally, the yield of the desired product **16a** was improved to 80% yield using 1.05 equivalents of AgOTf (entry 5). AgOTf was essential for this Friedel–Crafts-type reaction (entry 6).

After the construction of a tetracyclic ABCD ring skeleton containing an amidine, we turned our attention to the formation of an azepine ring (G ring). A treatment of compound **16a** with Tf_2O and pyridine gave compound **17a**

Table 1 Formation of a tetracyclic ABCD skeleton through a Friedel–Crafts-type reaction



12 (R = OH)
13 (R = OTf)
15 (R = OMe)

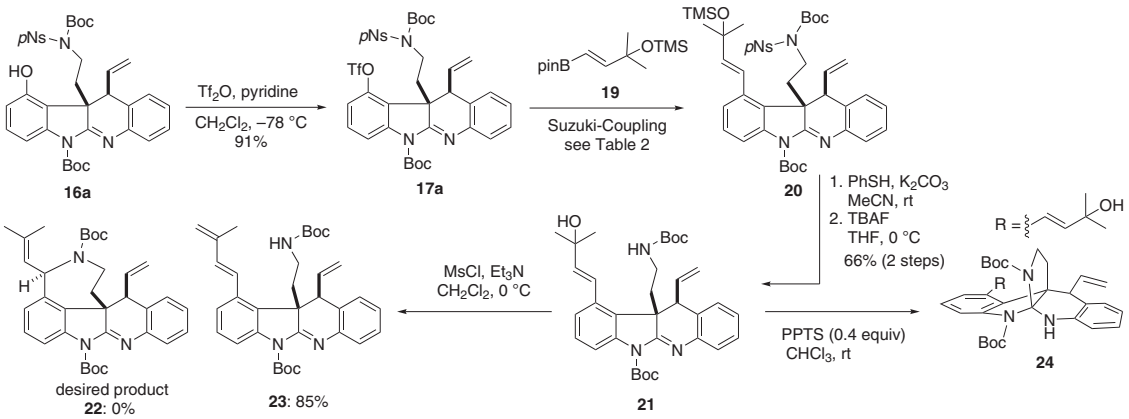
16a (R = OH)
17a (R = OTf)
18a (R = OMe)

16b (R = OH)
17b (R = OTf)
18b (R = OMe)

Entry	Starting material	X equiv	Yield	
1	**15** (R = OMe)	3.5	**18a**: 49%	**18b**: 30%
2	**13** (R = OTf)	3.5	**17a**: 0%	**17b**: 0%[a]
3	**12** (R = OH)	3.5	**16a**: 63%	**16b**: 30%
4	**12** (R = OH)	1.2	**16a**: 74%	**16b**: 17%
5	**12** (R = OH)	1.05	**16a**: 80%	**16b**: 13%
6	**12** (R = OH)	0	**16a**: 0%	**16b**: 0%[b]

[a]Complex mixture

[b]Starting material **12** was recovered in 77% yield



16a
17a
20
24
21
desired product
22: 0%
23: 85%

Scheme 3 Failed attempt at the formation of an azepine ring

in 91% yield (Scheme 3). To introduce an allyl alcohol unit, Suzuki–Miyaura coupling with vinyl boronic ester **19** was examined. When compound **17a** and vinyl boronic ester **19** were treated with a catalytic amount of $Pd(dba)_2$, SPhos and K_3PO_4, or $Pd(PPh_3)_4$ and Na_2CO_3 in *N*,*N*-dimethylformamide (DMF) at 100 °C, respectively, these reactions gave the desired product **20** in low yield (Table 2, entries 1 and 2). However, conditions involving $Pd(PPh_3)_4$ and Na_2CO_3 in toluene and ethanol at 100 °C improved the yield to 56% (entry 3). The removal of the *p*Ns and trimethylsilyl (TMS) group gave allyl alcohol **21** in 66% yield over two steps. To construct the azepine ring, mesylation of a tertiary alcohol was initially attempted through a treatment with methanesulfonyl chloride (MsCl) and Et_3N [18]. However, a dehydration occurred to give diene **23** instead of the desired

Table 2 Suzuki–Miyaura coupling of compound **17a** and boronate **19**

Entry	Cat.	Ligand	Base	Solvent	Temp.	Yield
1	$Pd(dba)_2$	SPhos	K_3PO_4	DMF	100 °C	10%
2	$Pd(PPh_3)_4$	–	aq. Na_2CO_3	DMF	100 °C	28%
3	$Pd(PPh_3)_4$	–	aq. Na_2CO_3	toluene/EtOH	100 °C	56%

cyclized product **22**. Interestingly, when compound **21** was treated with pyridinium *p*-toluenesulfonate (PPTS) [15], ortho-amide **24** was observed (as assessed using ^{1}H NMR analysis). A related structure was observed in synthetic studies of dehaloperophoramidine reported by Somfai et al. [13, 14]. We considered the thermodynamic stability of possible equilibrium products such as simplified

compounds **25**, **26,** and **27** through density functional theory (DFT) calculations (Fig. 2). These calculations revealed that ortho-amide **26** was the most stable isomer among these compounds. These results indicate that the formation of the ortho-amide through acid activation using PPTS from amidine would be a competitive process with the formation of the azepine ring via the S_N2' reaction of the tertiary alcohol, and the equilibrium tends to be biased toward the ortho-amides, such as compounds **24** and **26**. Therefore, we expected that it would be difficult to achieve the formation of azepine **22** from compound **21** containing the amidine moiety.

Therefore, a reduction of amidine **20** was investigated prior to the formation of the azepine ring to avoid the formation of the ortho-amide (Scheme 4). When compound **20** was treated with $NaBH_4$, the desired product was not obtained. In the case of DIBAL-H, the removal of a Boc group occurred instead of the reduction of the amidine. However, in sharp contrast, treatment with catechol borane [39] gave the desired product **28** in 65% yield as a 3.3:1 mixture of diastereomers. A NOESY experiment indicated that the stereochemistry of the major isomer was a *trans*-fused structure, which would be epimerized to a *cis*-fused structure later. Because a reducing reagent (catechol borane) would approach from the opposite side of the sterically hindered substituent ($-CH_2CH_2N(Boc)(p\text{Ns})$) of the angular position of the BC ring, the *trans* isomer was obtained as a major product in this reaction. After the removal of *p*Ns and the TMS groups, the formation of an azepine ring was investigated again. When compound **29** was treated with MsCl and Et_3N [18], the reaction gave diene **31** in 48% yield and the desired cyclized product **30** was not detected at all (Table 3, entry 1). When $Bi(OTf)_3$ was employed at −15 °C as a Lewis acid, the reaction proceeded to give the desired product **30** as a major product albeit in low yield (entry 2) [40, 41]. The reaction using $Bi(OTf)_3$ at −40 °C gave the desired product **30** in 17% yield with recovery of the starting material (entry 3). However, under room temperature reaction conditions, the starting material **29** was consumed completely to give the desired azepine **30** in 55% yield, while diene **31** was obtained in 34% yield (entry 4). The newly generated stereochemistry of compound **30** was confirmed to have the desired stereochemistry using NOESY experiments (Fig. 3a). In this cyclization, it was supposed that transition state **B** would not be favored than transition state **A** because of the presence of the steric repulsion between the allyl alcohol and vinyl group (Fig. 3b). Thus, compound **30** was obtained as a single diastereomer through transition state **A**. The obtained pentacyclic compound **30** would be useful for further derivatization, and now we are investigating further transformations to achieve a total synthesis of communesin F.

In summary, we have investigated the synthesis of a pentacyclic ABCDG ring skeleton of communesin F based on carboborylation of 1,3-diene, a $Bi(OTf)_3$-catalyzed

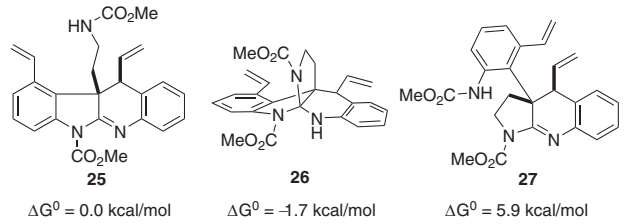


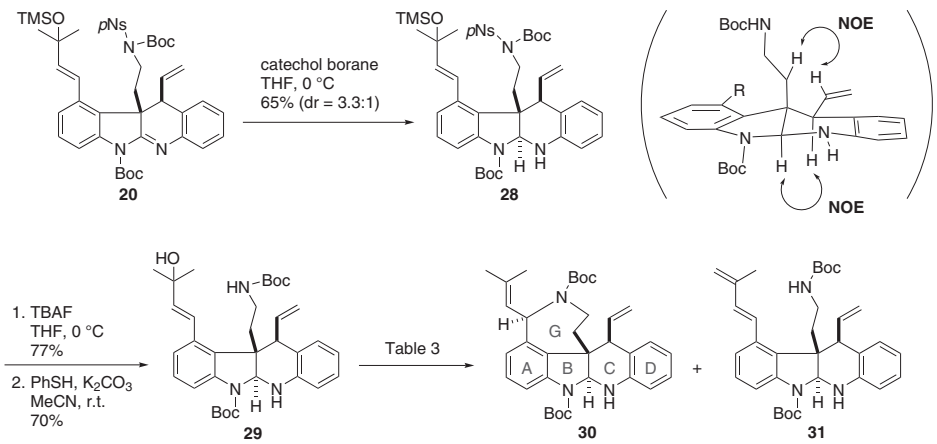
Fig. 2 Comparison of the thermodynamic stability of formable compounds **25**, **26,** and **27**, calculated using Gaussian '09 at the B3LYP/6-31G(d) level of theory (DFT)

Table 3 Investigation of the formation of the azepine ring

Entry	Conditions	Yield	
1	MsCl, Et_3N, CH_2Cl_2, 0 °C	**30**: 0%	**31**: 48%
2	$Bi(OTf)_3$ (10 mol%), MS4Å, CH_2Cl_2, −15 °C	**30**: 23%	**31**: trace
3	$Bi(OTf)_3$ (10 mol%), MS4Å, CH_2Cl_2, −40 °C	**30**: 17%	**31**: 0%[a]
4	$Bi(OTf)_3$ (10 mol%), MS4Å, CH_2Cl_2, 0 °C to rt	**30**: 55%	**31**: 34%

[a]Starting material **29** was recovered in 67% yield

Scheme 4 Synthesis of the ABCDG ring skeleton **30**



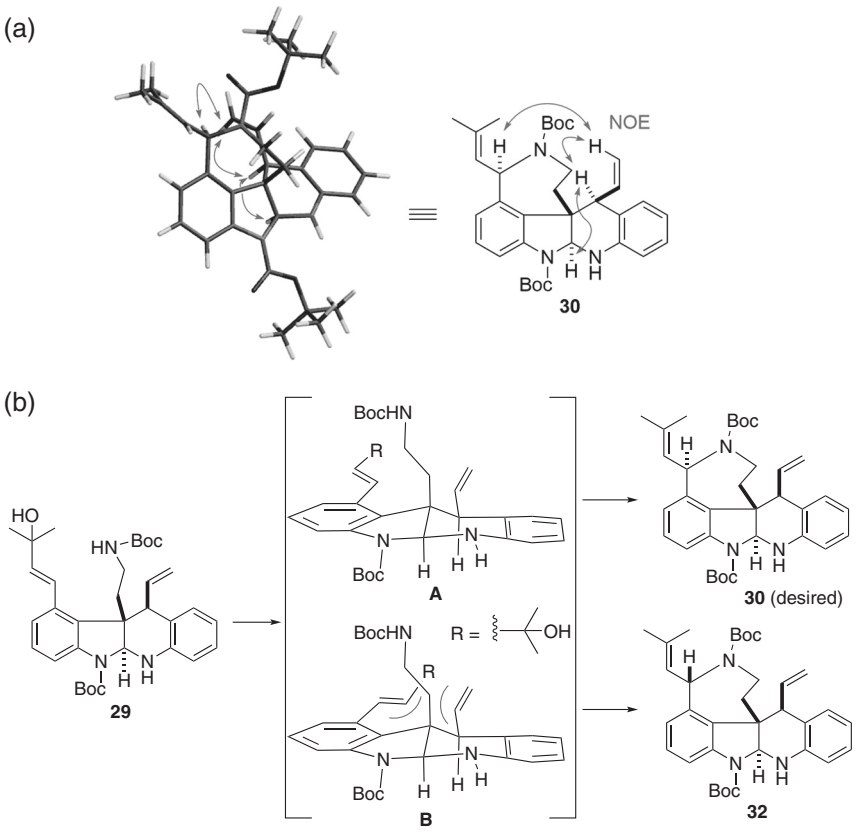


Fig. 3 **a** NOESY experiment of compounds **30**, **b** proposed transition state **A** and **B**

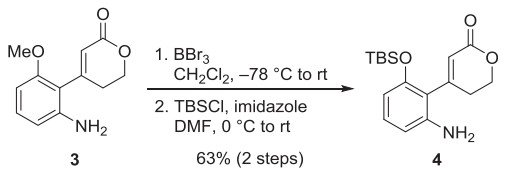
Friedel–Crafts-type reaction and azepine ring formation. It is interesting that a triflate group was intact under the conditions required for Pd-catalyzed carboborylation of 1,3-diene. Additionally, it was essential that the resultant amidine was reduced prior to the formation of the azepine ring through Bi $(OTf)_3$-catalyzed cyclization to avoid an undesired formation of ortho-amide. We are currently investigating further transformation of the pentacyclic compound to complete the synthesis of communesin F.

Experimental procedure

General

All non-aqueous reactions were carried out under a positive pressure of argon in oven-dried glassware. Analytical thin-layer chromatography was performed using Silica gel 60 plates (Merck, Darmstadt, Germany). Silica gel column chromatography was performed using Kanto silica gel 60 (particle size of 63–210 μm, Kanto, Tokyo, Japan) and Chromatorex BW-300 (Fuji silysia, Aichi, Japan). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a JNM-ECA 500 (JEOL, Tokyo, Japan) at 500 MHz or a JNM-AL 400 (JEOL) at 400 MHz. Chemical shifts were reported relative to Me_4Si (δ 0.00) in $CDCl_3$ or the residual solvent peak in C_6D_6 (δ 7.16). Multiplicity was indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a JNM-ECA 500 at 126 MHz or a JNM-AL 400 at 100 MHz. Chemical shifts were reported relative to $CDCl_3$ (δ 77.0) or C_6D_6 (δ 128.0). Infrared spectra were recorded using a FT/IR-4100 Fourier-transform infrared spectrometer (JASCO, Tokyo, Japan) with ATR (attenuated total reflectance). Low- and high-resolution mass spectra were recorded using a JMS-700 mass spectrometer (JEOL) for FAB-MS and a LCMS-IT-TOF (Shimadzu, Kyoto, Japan) for ESI-MS.

Experimental procedures and spectroscopic data

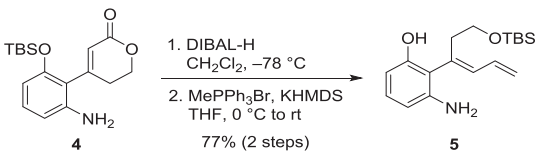


3 4

Silylether **4**: To a solution of aniline **3** (2.06 g, 9.40 mmol) in CH_2Cl_2 (94.0 mL) was added a solution of BBr_3 (25.0 g, 94.0 mmol) in CH_2Cl_2 (94.0 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min, and then warmed to room temperature. After 2 h, saturated aqueous $NaHCO_3$ and 1 M aqueous NaOH were added to the reaction mixture until the mixture became basic. The

mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a crude demethylated lactone.

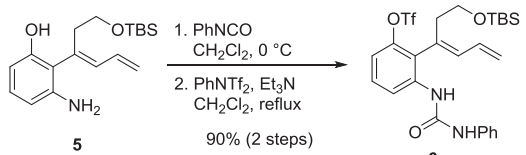
To a solution of the above crude lactone in anhydrous DMF (20.0 mL) were added TBSCl (2.80 g, 18.8 mmol) and imidazole (1.90 g, 28.2 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. After addition of water, the mixture was extracted with extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–40% EtOAc/hexane) gave silylether **4** (1.88 g, 63% in two steps) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, 1 H, J = 8.0, 8.0 Hz), 6.35 (dd, 1 H, J = 8.0, 1.1 Hz), 6.27 (dd, 1 H, J = 8.0, 1.1 Hz), 6.06 (dd, 1 H, J = 1.7, 1.2 Hz), 4.53 (dd, 2 H, J = 6.3, 5.8 Hz), 3.76 (br, 2 H), 2.72 (dd, 2 H, J = 6.3, 5.7 Hz), 0.94 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 156.1, 153.1, 144.0, 129.8, 120.3, 115.5, 108.7, 108.6, 66.5, 28.2, 25.6, 18.1, −4.1; IR (ATR, cm^{-1}) 3369, 2954, 2891, 2857, 1716, 1625, 1580, 1462, 1398, 1302, 1257, 1219, 1081, 1020; MS (FAB) *m/z* 320 $[M + H]^+$; HRMS calcd for $C_{17}H_{26}NO_3Si$ $[M + H]^+$ 320.1682; found: *m/z* 320.1685.



4 5

(*E*)-Dienylaniline **5**: To a solution of silylether **4** (1.25 g, 3.91 mmol) in CH_2Cl_2 (40.0 mL) was added DIBAL-H (1 M in toluene, 7.80 mL, 7.80 mmol) at −78 °C. After the mixture was stirred at −78 °C for 2 h, saturated aqueous Na/K tartrate was added to the reaction solution. The resultant mixture was stirred vigorously at room temperature for 2 h, and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a crude acetal.

To a suspension of $MePPh_3Br$ (4.89 g, 13.7 mmol) in anhydrous THF (25.0 mL) was added KHMDS (1 M solution in THF; 12.0 mL, 11.7 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. To the yellow mixture was then added a solution of the above crude acetal in anhydrous THF (15 mL) via cannula. The reaction mixture was stirred at room temperature for 2 h. After addition of water, the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–40% EtOAc/hexane) gave (*E*)-dienylaniline **5** (963.1 mg, 77% in two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dd, 1 H, J = 8.0, 8.0 Hz), 6.77 (ddd, 1 H, J = 16.9, 10.9, 10.3 Hz), 6.36 (dd, 1 H, J = 8.0, 0.8 Hz), 6.29 (d, 1 H, J = 11.1 Hz), 6.25 (dd, 1 H, J = 10.3 Hz), 5.27 (dd, 1 H, J = 16.9, 1.2 Hz), 5.24 (d, 1 H, J = 10.3 Hz), 3.75 (br, 1 H), 3.63 (br, 1 H), 3.60 (br, 2 H), 2.98 (br, 1 H), 2.38 (br, 1 H), 0.88 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 144.7, 136.6, 132.4, 132.1, 128.7, 119.3, 115.8, 106.9, 106.0, 60.6, 33.3, 25.7, 18.1, −5.5; IR (ATR, cm^{-1}) 3375, 2955, 2924, 2857, 1618, 1581, 1464, 1234, 1088; MS (FAB) *m/z* 320 $[M + H]^+$; HRMS calcd for $C_{18}H_{30}NO_2Si$ $[M + H]^+$ 320.2046; found: *m/z* 320.2045.

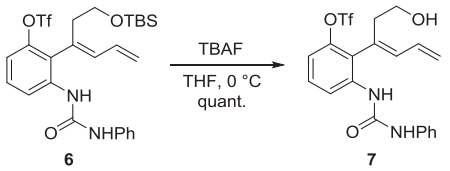


5 6

(*E*)-Dienylurea **6**: To a solution of (*E*)-dienylaniline **5** (847.9 mg, 2.65 mmol) in CH_2Cl_2 (26.0 mL) was added phenyl isocyanate (317.0 μL, 2.92 mmol) at 0 °C. The mixture was stirred at 0 °C for 13 h. After addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by short-column chromatography on silica gel (10–20% EtOAc/hexane) gave a crude urea as a white solid.

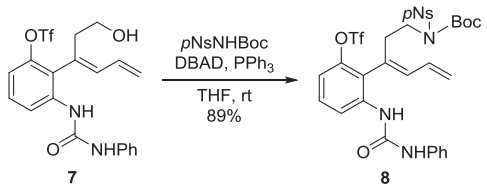
To a solution of the above crude urea in CH_2Cl_2 (50.0 mL) were added Et_3N (2.10 mL, 15.1 mmol) and $PhNTf_2$ (6.15 g, 17.2 mmol) in some portions. The resultant solution was refluxed at 55 °C for 3 days. The reaction mixture was then cooled to room temperature. After addition of saturated aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–20% EtOAc/hexane) gave (*E*)-dienylurea **6** (1.37 g, 90% in 2 steps) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, 1 H, J = 8.3, 0.9 Hz), 7.39 (br, 1 H), 7.34–7.30 (m, 5 H), 7.13–7.09 (m, 1 H), 9.97 (dd, 1 H, J = 8.3, 0.9 Hz), 6.69 (ddd, 1 H, J = 16.6, 10.9, 10.3 Hz), 6.65 (br, 1 H), 6.21 (d, 1 H, J = 11.1 Hz), 5.38–5.34 (m, 2 H), 3.71–3.69 (m, 1 H), 3.55–3.51 (m, 1 H), 2.97–2.95 (m, 1 H), 2.39–2.36 (m, 1 H), 0.83 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 147.2, 138.8, 137.6, 137.1, 131.4, 129.7, 129.3, 128.9, 126.8, 124.4, 121.4, 121.1, 120.6, 119.7, 118.4 (q, J = 321 Hz), 115.1, 61.6, 35.0, 25.9, 18.5, −5.5; IR (ATR, cm^{-1}) 3332, 2954, 2857, 1659, 1550, 1524, 1446, 1420, 1296, 1250, 1207, 1139, 1054, 962; MS (FAB) *m/z* 571 $[M + H]^+$; HRMS calcd for $C_{26}H_{34}F_3N_2O_5SSi$ $[M + H]^+$ 571.1910; found: *m/z*

571.1910.



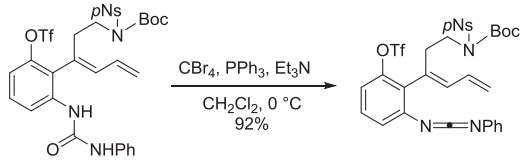
6 7

(*E*)-Dienylalcohol **7**: To a solution of (*E*)-dienylurea **6** (42.7 mg, 0.0748 mmol) in THF (1.0 mL) was added TBAF (1 M in THF, 83.0 μL, 0.083 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After addition of saturated aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (10–40% EtOAc/hexane) gave (*E*)-dienylalcohol **7** (35.3 mg, quant.) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 1 H, J = 8.6 Hz), 7.77 (br, 1 H), 7.32–7.18 (m, 5 H), 7.18 (br, 1 H), 7.07 (dd, 1 H, J = 7.1, 6.9 Hz), 6.94 (d, 1 H, J = 8.3 Hz), 6.72 (ddd, 1 H, J = 16.9, 10.9, 10.3 Hz), 6.24 (d, 1 H, J = 10.9 Hz), 5.39–5.33 (m, 2 H), 3.81 (br, 1 H), 3.46 (br, 1 H), 3.04 (br, 1 H), 2.35 (d, 1 H, J = 14.6 Hz), 2.23 (br, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 147.3, 139.3, 137.9, 137.8, 131.3, 129.2, 129.1, 129.1, 126.1, 124.1, 121.4, 120.9, 119.6, 118.4 (q, J = 321 Hz), 114.8, 60.2, 34.2; IR (ATR, cm^{-1}) 3337, 3010, 2926, 1670, 1579, 1550, 1446, 1420, 1297, 1210, 1138, 1051, 963; MS (FAB) *m/z* 457 $[M + H]^+$; HRMS calcd for $C_{20}H_{20}F_3N_2O_5S$ $[M + H]^+$ 457.1045; found: *m/z* 457.1042.



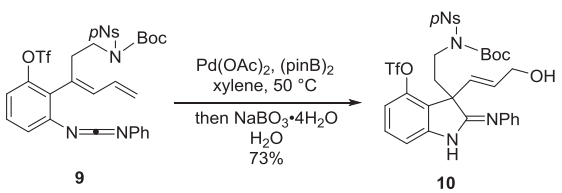
7 8

(*E*)-Dienylurea **8**: To a solution of (*E*)-dienylalcohol **7** (992.0 mg, 2.17 mmol), *p*NsNHBoc (786.0 mg, 2.60 mmol) and PPh_3 (682.0 mg, 2.60 mmol) in THF (12.0 mL) was added a solution of di-*tert*-butyl azodicarboxylate (598.7 mg, 2.60 mmol) in THF (10.0 mL). The mixture was stirred at room temperature for 13.5 h. After addition of saturated aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (10–40% EtOAc/hexane) gave the mixture of (*E*)-dienylurea **8** and *p*NsNHBoc. The mixture was dissolved in $CHCl_3$, washed with 1 M aqueous NaOH and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave (*E*)-dienylurea **8** (1.43 g, 89%) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35–8.32 (m, 3 H), 8.04 (d, 2 H, J = 9.1 Hz), 7.47 (br, 1 H), 7.37–7.29 (m, 5 H), 7.17 (br, 1 H), 7.13–7.09 (m, 1 H), 6.98 (d, 1 H, J = 8.3 Hz), 6.79 (ddd, 1 H, J = 16.3, 10.9, 10.6 Hz), 6.24 (d, 1 H, J = 10.9 Hz), 5.42–5.38 (m, 2 H), 3.88–3.78 (m, 2 H), 3.15–3.09 (m, 1 H), 2.76–2.70 (m, 1 H), 1.32 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 150.9, 150.5, 147.3, 145.1, 138.5, 138.4, 137.7, 131.3, 129.4, 129.4, 129.1, 128.1, 125.9, 124.6, 124.1, 122.6, 121.3, 120.0, 118.4 (q, J = 321 Hz), 115.1, 86.5, 46.2, 33.4, 27.9; IR (ATR, cm^{-1}) 3349, 2929, 2854, 1732, 1668, 1534, 1446, 1420, 1368, 1351, 1291, 1249, 1212, 1139, 1055, 961; MS (FAB) *m/z* 741 $[M + H]^+$; HRMS calcd for $C_{31}H_{32}F_3N_4O_{10}S_2$ $[M + H]^+$ 741.1512; found: *m/z* 741.1512.



8 9

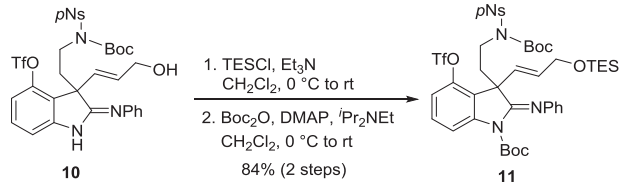
(*E*)-Dienylcarbodiimide **9**: To a solution of (*E*)-dienylurea **8** (62.5 mg, 0.0844 mmol) and PPh_3 (73.5 mg, 0.270 mmol) in CH_2Cl_2 (2.0 mL) were added Et_3N (47.0 μL, 0.338 mmol) and CBr_4 (83.9 mg, 0.253 mmol) at 0 °C. The mixture was stirred at 0 °C for 2.5 h. After concentration of the mixture under reduced pressure, purification of the residue by flash column chromatography on neutral silica gel (5–20% EtOAc/hexane) gave (*E*)-dienylcarbodiimide **9** (56.4 mg, 92%) as a pale yellow oil. The product was not stable, thus it was used for the next reaction immediately: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, 2 H, J = 8.9 Hz), 8.07 (d, 2 H, J = 8.8 Hz), 7.37–7.27 (m, 4 H), 7.19 (dd, 1 H, J = 7.5, 7.4 Hz), 7.16–7.13 (m, 3 H), 6.80 (ddd, 1 H, J = 16.6, 10.6, 10.6 Hz), 6.25 (d, 1 H, J = 11.2 Hz), 5.37–5.32 (m, 2 H), 3.89 (dd, 2 H, J = 7.2, 7.2 Hz), 2.99 (br, 2 H), 1.31 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 150.2, 147.6, 145.4, 139.3, 137.3, 137.2, 132.4, 132.1, 131.1, 129.5, 129.3, 129.1, 127.9, 125.9, 124.9, 124.4, 123.9, 121.6, 118.4 (q, J = 321 Hz), 118.2, 85.2, 45.9, 33.4, 27.7; IR (ATR, cm^{-1}) 3105, 2938, 2857, 2141, 1731, 1591, 1563, 1533, 1476, 1452, 1421, 1366, 1351, 1285, 1250, 1213, 1137, 909 (Compound **9** was too unstable to measure HRMS).



9 10

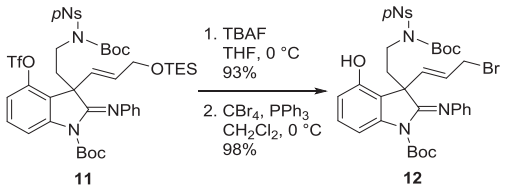
2-Iminoindoline **10**: To a solution of carbodiimide **9** (56.4 mg, 0.0780 mmol) in anhydrous xylene (1.0 mL) were added bis(pinacolato)diboron (39.6 mg, 0.156 mmol) and $Pd(OAc)_2$ (3.5 mg, 0.0156 mmol) and the reaction

atmosphere was replaced by the Ar atmosphere. The mixture was stirred at 50 °C for 1 h, and then cooled to 0 °C. After addition of water (1.0 mL) and sodium perborate tetrahydrate (72.0 mg, 0.468 mmol), the mixture was stirred vigorously at room temperature for 1 h. The mixture was then extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (20–60% EtOAc/hexane) gave 2-iminoindoline **10** (42.4 mg, 73%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2 H, J = 8.9 Hz), 7.94 (d, 2 H, J = 8.9 Hz), 7.79 (d, 2 H, J = 8.0 Hz), 7.40–7.34 (m, 4 H), 7.13 (dd, 1 H, J = 7.5, 7.4 Hz), 6.98 (br, 1 H), 6.93–6.90 (m, 1 H), 6.07 (ddd, 1 H, J = 15.8, 5.2, 4.8 Hz), 5.78 (d, 1 H, J = 16.0 Hz), 4.23 (d, 2 H, J = 4.9 Hz), 3.45 (ddd, 1 H, J = 14.0, 11.8, 4.0 Hz), 3.22 (ddd, 1 H, J = 14.3, 12.0, 4.3 Hz), 2.89 (ddd, 1 H, J = 12.6, 12.6, 4.3 Hz), 2.54 (ddd, 1 H, J = 12.6, 12.4, 4.0 Hz), 1.94 (br, 1 H), 1.31 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 158.9, 150.3, 150.0, 145.1, 144.9, 138.6, 133.2, 131.1, 129.2, 129.1, 127.6, 127.5, 124.1, 123.9, 120.0, 118.5 (q, J = 320 Hz), 117.9, 114.4, 85.7, 62.8, 59.0, 43.4, 33.0, 27.7; IR (ATR, cm^{-1}) 3380, 3106, 2936, 2877, 1732, 1561, 1534, 1439, 1420, 1349, 1247, 1213, 1138, 1083, 1014, 907; MS (FAB) *m/z* 741 [M + H]$^+$; HRMS calcd for $C_{31}H_{32}F_3N_4O_{10}S_2$ [M + H]$^+$ 741.1512; found: *m/z* 741.1508.



N-Boc-iminoindoline **11**: To a solution of 2-iminoindoline **10** (39.4 mg, 0.0532 mmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (23.0 μL, 0.160 mmol) and TESCl (16.0 μL, 0.106 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. After addition of water, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by short-column chromatography on neutral silica gel (10–30% EtOAc/hexane) gave a crude TES-protected iminoindoline.

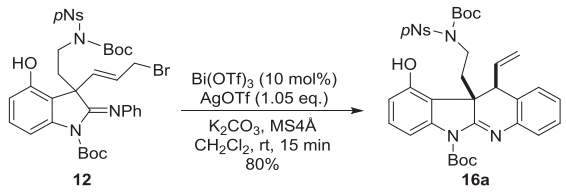
To a solution of the above crude iminoindoline in CH_2Cl_2 (1.0 mL) were added Pr_2NEt (37.0 μL, 0.213 mmol), Boc_2O (34.9 mg, 0.160 mmol), and DMAP (6.5 mg, 0.0532 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h. After concentration of the resultant mixture under reduced pressure, purification of the residue by flash column chromatography on silica gel (10–30% EtOAc/hexane) gave *N*-Boc-iminoindoline **11** (33.7 mg, 84% in two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2 H, J = 8.9 Hz), 8.05 (d, 2 H, J = 8.8Hz), 7.73 (d, 1 H, J = 8.0 Hz), 7.41 (dd, 1 H, J = 8.6, 8.3 Hz), 7.31 (dd, 2 H, J = 7.8, 7.7 Hz) 7.12 (d, 1 H, J = 8.3 Hz), 7.06–7.02 (m, 3 H), 5.93 (d, 1 H, J = 15.5 Hz), 5.66 (d, 1 H, J = 15.5 Hz), 4.17 (d, 2 H, J = 4.3 Hz), 3.85–3.79 (m, 1 H), 3.65–3.62 (m, 1 H), 2.70–2.63 (m, 2 H), 1.27 (s, 9 H), 1.18 (s, 9 H), 0.92 (dd, 9 H, J = 8.0, 7.8Hz), 0.57 (q, 6 H, J = 7.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 150.2, 150.1, 149.0, 147.9, 145.9, 145.6, 143.5, 131.5, 130.5, 129.4, 129.1, 128.7, 123.9, 123.8, 122.1, 120.5, 118.3 (q, J = 321 Hz), 115.8, 114.1, 85.3, 84.8, 62.6, 54.0, 43.2, 34.7, 27.7, 27.4, 6.7, 4.3; IR (ATR, cm^{-1}) 2955, 2876, 1731, 1698, 1617, 1594, 1535, 1456, 1421, 1370, 1348, 1287, 1251, 1218, 1141, 1046, 1014, 917, 822; MS (FAB) *m/z* 955 [M + H]$^+$; HRMS calcd for $C_{42}H_{54}F_3N_4O_{12}S_2Si$ [M + H]$^+$ 955.2901; found: *m/z* 955.2900.



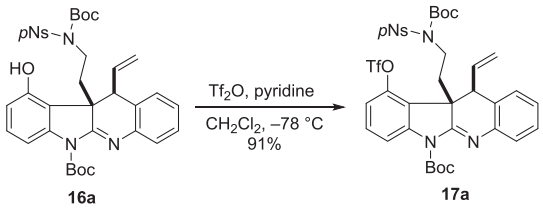
Allyl bromide **12**: To a solution of *N*-Boc-iminoindoline **11** (21.9 mg, 0.0229 mmol) in THF (0.5 mL) was added TBAF (48.1 μL, 0.0481 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. After addition of saturated aqueous NH_4Cl, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (20–60% EtOAc/hexane) gave an allyl alcohol (15.1 mg, 93%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, 2 H, J = 8.8 Hz), 8.07 (d, 2 H, J = 8.8 Hz), 7.29 (dd, 2 H, J = 7.5, 7.2 Hz), 7.19 (d, 1 H, J = 7.7 Hz), 7.13–7.09 (m, 1 H) 7.04–6.99 (m, 3 H), 6.59 (d, 1 H, J = 8.0 Hz), 6.03 (d, 1 H, J = 15.1 Hz), 5.77 (d, 1 H, J = 15.4 Hz), 4.09 (br, 2 H), 3.86–3.80 (m, 1 H), 3.69–3.63 (m, 1 H), 2.78 (ddd, 1 H, J = 12.3, 12.1, 4.6 Hz), 2.58 (ddd, 1 H, J = 12.1, 12.0, 4.3 Hz), 1.27 (s, 9 H), 1.21 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 152.7, 150.3, 150.2, 149.2, 148.4, 145.5, 142.2, 131.3, 129.8, 129.6, 129.4, 129.1, 123.8, 123.7, 120.4, 115.2, 112.7, 106.6, 85.2, 84.2, 62.9, 53.5, 43.9, 35.2, 27.7, 27.5; IR (ATR, cm^{-1}) 3445, 2980, 1729, 1695, 1535, 1450, 1360, 1352, 1270, 1085, 910, 730; MS (FAB) *m/z* 709 [M + H]$^+$; HRMS calcd for $C_{35}H_{41}N_4O_{10}S$ [M + H]$^+$ 709.2543; found: *m/z* 709.2543.

To a solution of the above allyl alcohol (169.6 mg, 0.239 mmol) and PPh_3 (157.4 mg, 0.598 mmol) in CH_2Cl_2 (2.5 mL) was added CBr_4 (158.5 mg, 0.478 mmol) at 0 °C.

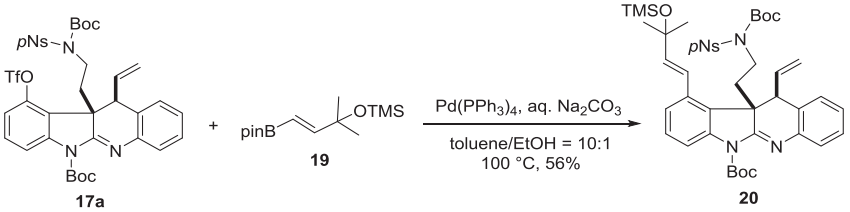
The mixture was stirred at 0 °C for 30 min. After addition of water, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (10–40% EtOAc/hexane) gave allyl bromide **12** (180.3 mg, 98%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2 H, J = 8.6 Hz), 8.08 (d, 2 H, J = 8.8 Hz), 7.32 (dd, 2 H, J = 8.0, 7.7 Hz), 7.32–7.27 (m, 1 H), 7.21–7.17 (m, 1 H) 7.07–7.02 (m, 3 H), 6.63 (d, 1 H, J = 8.0 Hz), 6.05 (d, 1 H, J = 15.2 Hz), 5.87–5.81 (m, 1 H), 3.96–3.89 (m, 2 H), 3.82 (ddd, 1 H, J = 14.7, 11.1, 4.6 Hz), 3.67 (dd, 1 H, J = 12.0, 11.2 Hz), 2.77 (dd, 1 H, J = 12.3, 10.9 Hz), 2.58 (ddd, 1 H, J = 12.3, 12.0, 4.3 Hz), 1.29 (s, 9 H), 1.20 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 152.2, 150.3, 150.2, 149.2, 148.3, 145.5, 142.4, 134.6, 130.1, 129.4, 129.1, 126.8, 123.8, 120.5, 114.8, 112.8, 107.4, 107.3, 85.3, 84.2, 53.5, 43.8, 34.8, 32.1, 27.8, 27.4; IR (ATR, cm^{-1}) 3445, 2980, 1729, 1695, 1599, 1532, 1460, 1366, 1348, 1277, 1250, 1143, 1085, 1061, 968, 909, 852, 730, 605, 578; MS (FAB) *m/z* 771 $[M + H]^+$; HRMS calcd for $C_{35}H_{40}BrN_4O_9S$ $[M + H]^+$ 771.1699; found: *m/z* 771.1696.



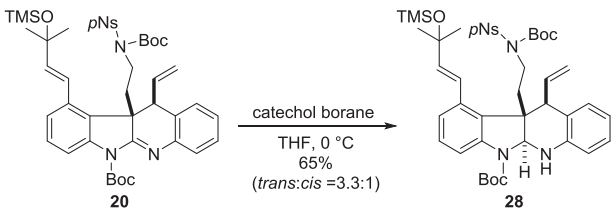
Tetracyclic compound **16a**: To a suspension of allyl bromide **12** (300.0 mg, 0.389 mmol), $Bi(OTf)_3$ (25.5 mg, 0.0389 mmol), AgOTf (104.8 mg, 0.408 mmol), MS4Å (300 mg), and K_2CO_3 (161.7 mg, 1.17 mmol) in CH_2Cl_2 (40.0 mL) was stirred at room temperature for 15 min. After addition of water, the mixture was then filtered through Celite pad. The filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (10–60% EtOAc/hexane) gave a tetracyclic compound **16a** (215.8 mg, 80%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, 2 H, J = 8.8 Hz), 7.89 (d, 2 H, J = 8.9 Hz), 7.52 (d, 1 H, J = 8.3 Hz), 7.41 (dd, 1 H, J = 7.8, 1.1 Hz), 7.36 (dd, 1 H, J = 7.5, 7.4 Hz), 7.24 (ddd, 1 H, J = 8.3, 8.3, 0.8 Hz), 7.18 (dd, 1 H, J = 7.5, 7.4 Hz), 7.13 (d, 1 H, J = 7.4 Hz), 6.69 (d, 1 H, J = 8.0 Hz), 6.48 (ddd, 1 H, J = 17.4, 10.0, 9.1 Hz), 5.81 (d, 1 H, J = 9.1 Hz), 5.67 (d, 1 H, J = 17.5 Hz), 4.00 (d, 1 H, J = 9.7 Hz), 3.57–3.50 (m, 1 H), 3.26–3.20 (m, 1 H), 2.19–2.11 (m, 2 H), 1.70 (s, 9 H), 1.26 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 152.9, 150.2, 149.9, 149.3, 145.0, 143.6, 142.9, 136.2, 130.7, 129.5, 128.6, 126.5, 126.0, 125.8, 125.1, 124.7, 123.8, 114.5, 114.2, 108.0, 85.1, 84.2, 50.1, 47.9, 43.8, 28.2, 27.7, 27.3; IR (ATR, cm^{-1}) 3449, 2979, 2919, 1731, 1654, 1599, 1533, 1460, 1368, 1348, 1282, 1236, 1148, 1088, 889,; MS (FAB) *m/z* 691 $[M + H]^+$; HRMS calcd for $C_{35}H_{39}N_4O_9S$ $[M + H]^+$ 691.2438; found: *m/z* 691.2439.



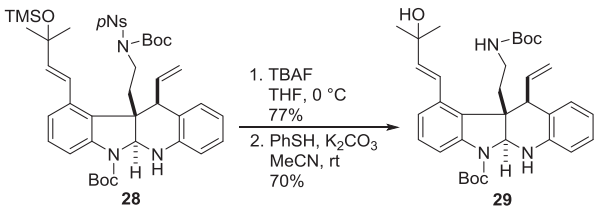
Triflate **17a**: To a solution of tetracyclic compound **16a** (213.0 mg, 0.308 mmol) in CH_2Cl_2 (5.0 mL) were added pyridine (87.3 μL, 1.08 mmol) and Tf_2O (103.5 μL, 0.616 mmol) at 0 °C. The mixture was stirred at 0 °C for 2.5 h. After addition of water, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–20% EtOAc/hexane) gave triflate **17a** (230.3 mg, 91%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, 2 H, J = 8.6 Hz), 7.97 (d, 1 H, J = 8.3 Hz), 7.91 (d, 2 H, J = 8.9 Hz), 7.45 (dd, 1 H, J = 8.6, 8.3 Hz), 7.37–7.32 (m, 2 H), 7.23-7.14 (m, 3 H), 6.28 (ddd, 1 H, J = 16.9, 10.0, 9.8 Hz), 5.55 (d, 1 H, J = 10.0 Hz), 5.30 (d, 1 H, J = 16.9 Hz), 3.88 (d, 1 H, J = 9.7 Hz), 3.53-3.49 (m, 1 H), 3.38-3.32 (m, 1 H), 2.26-2.22 (m, 2 H), 1.70 (s, 9 H), 1.27 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 150.2, 149.7, 149.1, 147.1, 145.2, 144.5, 143.4, 133.6, 131.0, 129.5, 128.4, 126.8, 126.3, 125.7, 125.5, 123.8, 121.5, 119.5, 118.2 (q, J = 318 Hz), 114.9, 114.3, 85.3, 84.8, 51.0, 48.1, 43.2, 28.1, 27.8, 27.6; IR (ATR, cm^{-1}) 2982, 2933, 1729, 1661, 1613, 1534, 1455, 1423, 1369, 13647, 1291, 1217, 1143, 1086, 1033, 922; MS (FAB) *m/z* 823 $[M + H]^+$; HRMS calcd for $C_{36}H_{38}F_3N_4O_{11}S_2$ $[M + H]^+$ 823.1931; found: *m/z* 823.1929.



Coupling product **20**: To a solution of triflate **17a** (30.0 mg, 0.0365 mmol) and vinyl boronate **19** (20.8 mg, 0.0730 mmol) in toluene (1.0 mL) and EtOH (0.1 mL) were added 0.5 M aqueous Na_2CO_3 (220.0 μL, 0.110 mmol) and Pd $(PPh_3)_4$ (4.2 mg, 3.65×10^{-3} mmol). The reaction atmosphere was replaced by the Ar atmosphere, and the mixture was stirred at 100 °C for 7 h. After the reaction mixture was then cooled to room temperature, the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–20% EtOAc/hexane) gave coupling product **20** (16.9 mg, 56%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, 2 H, J = 8.9 Hz), 7.86 (d, 2 H, J = 9.2 Hz), 7.35–7.31 (m, 5 H), 7.18–7.17 (m, 2 H), 6.90 (d, 1 H, J = 15.5 Hz), 6.30 (ddd, 1 H, J = 16.9, 10.1, 10.0 Hz), 6.13 (d, 1 H, J = 15.7 Hz), 5.48 (dd, 1 H, J = 10.0, 1.5 Hz), 5.27 (d, 1 H, J = 16.9 Hz), 3.85 (d, 1 H, J = 10.0 Hz), 3.41 (ddd, 1 H, J = 14.3, 13.7, 4.0 Hz), 3.26–3.19 (m, 1 H), 2.29 (ddd, 1 H, J = 12.9, 12.8, 5.5 Hz), 2.16 (ddd, 1 H, J = 12.9, 12.0, 4.0 Hz), 1.67 (s, 9 H), 1.68 (s, 3 H), 1.30 (s, 3 H), 1.29 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 149.8, 149.6, 149.7, 145.2, 144.1, 142.6, 139.0, 136.1, 134.6, 129.4, 129.0, 128.2, 126.7, 126.3, 125.7, 125.3, 125.3, 125.0, 123.8, 123.7, 122.5, 122.4, 113.5, 85.1, 84.0, 74.0, 51.5, 48.1, 44.3, 30.1, 30.1, 28.2, 27.9, 2.6; IR (ATR, cm^{-1}) 2978, 1727, 1655, 1597, 1575, 1533, 1474, 1452, 1368, 1347, 1291, 1249, 1150, 1087, 1034, 840, 748, 713, 685, 628, 602; MS (FAB) *m/z* 831 $[M + H]^+$; HRMS calcd for $C_{43}H_{55}N_4O_9SSi$ $[M + H]^+$ 831.3459; found: *m/z* 831.3448.



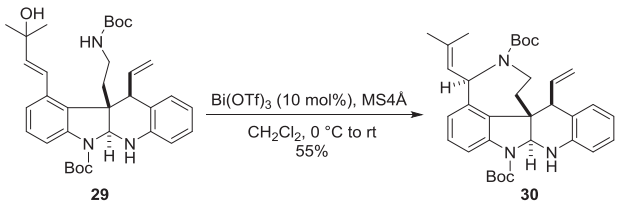
Aminal **28**: To a solution of coupling product **20** (50.0 mg, 0.0602 mmol) in THF (6.0 mL) was added catechol borane solution (1 M in THF, 75.3 μL, 0.0753 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. After addition of water, the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–20% EtOAc/hexane) gave aminal **28** (32.6 mg, 65%, dr = 3.3:1) as a yellow oil: (major diastereomer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, 2 H, J = 8.9 Hz), 7.93 (d, 2 H, J = 8.9 Hz), 7.75 (br, 1 H), 7.30 (d, 1 H, J = 8.0 Hz), 7.27–7.24 (m, 1 H), 7.20–7.14 (m, 2 H), 7.06 (d, 1 H, J = 15.8 Hz), 6.89 (dd, 1 H, J = 7.8, 7.4 Hz), 6.83 (d, 1 H, J = 8.0 Hz), 6.07 (d, 1 H, J = 15.8 Hz), 6.05–5.98 (m, 2 H), 5.61 (dd, 1 H, J = 10.0, 1.7 Hz), 5.35 (dd, 1 H, J = 16.9, 1.5 Hz), 4.89 (s, 1 H), 4.15 (d, 1 H, J = 10.3 Hz), 4.13–4.08 (m, 1 H), 3.29 (ddd, 1 H, J = 14.1, 14.1, 4.0 Hz), 2.08 (ddd, 1 H, J = 12.6, 12.6, 4.3 Hz), 1.86 (ddd, 1 H, J = 12.9, 12.9, 4.3 Hz), 1.65 (s, 9 H), 1.64 (s, 3 H), 1.28 (s, 3 H), 1.25 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 150.2, 145.7, 144.7, 140.6, 137.8, 137.1, 131.5, 129.5, 129.2, 128.9, 127.8, 127.7, 127.0, 125.4, 123.8, 123.7, 123.5, 121.9, 120.1, 116.9, 113.7, 84.6, 83.3, 78.3, 74.1, 54.8, 50.6, 44.8, 30.6, 30.4, 28.6, 27.9, 2.8; IR (ATR, cm^{-1}) 2997, 2918, 1731, 1696, 1534, 1467, 1370, 1347, 1235, 1089, 887, 627; MS (FAB) *m/z* 833 $[M + H]^+$; HRMS calcd for $C_{43}H_{57}N_4O_9SSi$ $[M + H]^+$ 833.3616; found: *m/z* 833.3616.



Aminal **29**: To a solution of aminal **28** (10.8 mg, 0.0130 mmol) in THF (1.3 mL) was added TBAF (1 M in THF, 15.6 μL, 0.0156 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h. After addition of saturated aqueous NH_4Cl, the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–30% EtOAc/hexane) gave an alcohol (7.6 mg, 77%) as a yellow oil.

To a solution of the above alcohol (7.6 mg, 9.99×10^{-3} mmol) in MeCN (1.0 mL) were added K_2CO_3 (9.6 mg, 0.0695 mmol) and PhSH (6.3 μL, 0.0614 mmol). The mixture was stirred at room temperature for 12 h, and then diluted with EtOAc. The organic layer was washed with water and brine, and then dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–30% EtOAc/hexane) gave aminal **29** (4.0 mg, 70%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br, 1 H), 7.33-7.26 (m, 2 H), 7.21 (dd, 1 H, J = 8.0, 8.0 Hz), 7.14–7.10 (m, 2 H), 6.84 (ddd, 1 H, J = 7.8, 7.8, 1.2 Hz), 6.78 (d, 1 H, J = 7.7 Hz), 6.14–6.07 (m, 2 H), 5.97 (br, 1 H), 5.61 (dd, 1 H, J = 10.0, 1.7 Hz), 5.40 (dd, 1 H, J = 17.2, 1.8 Hz), 4.85 (s, 1 H), 4.40 (br, 1 H), 4.15 (d, 1 H, J = 9.7 Hz), 2.94 (br, 1 H), 2.73 (br, 1 H), 1.93 (br, 1 H), 1.86 (br, 1 H), 1.63 (s, 9 H), 1.44 (s, 3 H), 1.40 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 144.7, 142.9, 140.7, 139.3, 137.2, 131.3, 129.9, 129.1, 128.8, 127.6, 127.3, 124.0, 122.9,

120.9, 120.1, 117.2, 113.9, 83.2, 78.9, 78.4, 71.2, 55.5, 50.8, 37.1, 30.2, 29.3, 28.53, 28.49; IR (ATR, cm^{-1}) 2978, 2916, 1469, 1384, 1283, 1234, 1089, 888, 628; MS (FAB) *m/z* 576 $[M + H]^+$; HRMS calcd for $C_{34}H_{45}N_3O_5$ $[M]^+$ 575.3359; found: *m/z* 575.3359.



Pentacyclic compound **30**: To a mixture of aminal **29** (6.9 mg, 0.0120 mmol) and MS4Å (7.0 mg) in CH_2Cl_2 (1.2 mL) was added $Bi(OTf)_3$ (0.8 mg, 1.2×10^{-3} mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, and then warmed to room temperature and stirred for 1 h. After addition of saturated aqueous $NaHCO_3$, and the mixture was diluted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5–20% EtOAc/hexane) gave a pentacyclic compound **30** (3.7 mg, 55%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (br, 1 H), 7.23-7.18 (m, 2 H), 7.11 (dd, 1 H, $J = 7.2$, 7.1 Hz), 7.00 (d, 1 H, $J = 7.8$ Hz), 6.81 (dd, 1 H, $J = 8.3$, 7.9 Hz), 6.75 (d, 1 H, $J = 8.0$ Hz), 5.94 (d, 1 H, $J = 9.2$ Hz), 5.92–5.88 (m, 1 H), 5.84 (br, 1 H), 5.42 (dd, 1 H, $J = 16.6$, 2.3 Hz), 5.38 (dd, 1 H, $J = 9.5$, 2.3 Hz), 5.05 (s, 1 H), 5.00 (d, 1 H, $J = 8.3$ Hz), 4.10 (d, 1 H, $J = 10.0$ Hz), 3.90 (dd, 1 H, $J = 14.0$, 4.0 Hz), 2.10 (ddd, 1 H, $J = 14.6$, 11.4, 5.4 Hz), 2.03-1.96 (m, 2 H), 1.85 (s, 3 H), 1.65 (s, 3 H), 1.63 (s, 9 H), 1.46 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 153.8, 144.7, 142.8, 138.5, 137.7, 132.7, 131.2, 130.7, 128.2, 127.6, 126.0, 124.7, 122.8, 120.0, 118.2, 116.7, 114.6, 82.8, 79.2, 78.7, 58.7, 58.2, 50.7, 41.0, 28.5, 28.4, 25.2, 23.5, 18.4; IR (ATR, cm^{-1}) 2977, 2919, 1691, 1466, 1391, 1341, 1279, 1235, 1089, 889, 756, 628, 523; MS (FAB) *m/z* 558 $[M + H]^+$; HRMS calcd for $C_{34}H_{42}N_3O_4$ $[M - H]^-$ 556.3175; Found: *m/z* 556.3177. (ESI) HRMS calcd for $C_{34}H_{44}N_3O_4$ $[M + H]^+$ 558.3332; found: *m/z* 558.3311.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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