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Evolution of a Strategy for Total Synthesis of the Marine Fungal Alkaloid (±)-Communesin F

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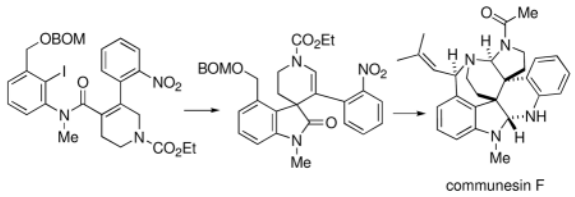
Abstract



communesin F

A new synthetic strategy for construction of the heptacyclic marine fungal alkaloid (±)-communesin F has been devised. Key reactions include an intramolecular Heck cyclization of a tetrasubstituted alkene to generate a tetracyclic enamide bearing one of the quaternary carbon centers (C7) of the alkaloid, an intramolecular reductive cyclization of an N-Boc aniline onto the oxindole moiety to form a pentacyclic framework containing the southern aminal, a stereoselective N-Boc-lactam enolate C-allylation to introduce the second quaternary carbon center (C8), and an azide reduction/N-Boc-lactam-opening cascade leading to the northern aminal.

Introduction and Background

Marine microbes are a relatively new source of unique natural products, in contrast to terrestrial microorganisms, which have been studied extensively for many decades. In 1993 Numata and coworkers reported two structurally unique polycyclic alkaloids, communesin A (**1**) and B (**5**) which were isolated from a *Penicillium* fungus growing on the marine alga *Enteromorpha intestinalis* (Figure 1).[1] Communesins A (**1**) and B (**5**) show cytotoxicity against P-388 lymphocytic leukemia cells with moderate to potent activity (ED_{50} = 3.5 μg/mL and 0.45 μg/mL, respectively). The structures of these alkaloids were elucidated by extensive spectroscopic analysis. Thus, the communesins have a novel heptacyclic skeleton bearing two aminal functional groups, two vicinal quaternary carbon centers (C7, C8) and an epoxide moiety. The relative stereochemistry of the communesins (except for C21) was determined by NMR nOe studies, although the absolute configurations of **1** and **5** could not be established at that time.

In 2003, Hemscheidt and coworkers described an alkaloid, nomofungin (**9**), which was isolated from the fermentation broth of an unidentified fungus derived from the bark of *Ficus microcarpa* L., growing on the Manoa campus of the University of Hawaii.[2] The name, nomofungin, was chosen because the fungus producing this alkaloid was lost after isolation of the metabolite. Although nomofungin and communesin B (**5**) have identical ^{1}H and ^{13}C NMR spectral data, the metabolite was initially proposed to have structure **9**, which has a lower N,O-

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Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds and experimental procedures for some sequences. This material is available free of charge on the Internet at http://pubs.acs.org.

acetal rather than the aminal of communesin B. However, it was later found that this assignment was incorrect, and that nomofungin is actually communesin B (**5**). It should be noted that the Hemscheidt studies did establish both the configuration at C21 of **5** using Murata's *J*-based NMR method, as well as the absolute configuration of the molecule using the exciton chirality method as being 6*R*, 7*R*, 8*R*, 9*S*, 11*S*, 21*R* as shown. Hemscheidt also found that communesin B has cytotoxic activity against LoVo and KB cells (MIC 2.0 μg/mL, 4.5 μg/mL, respectively), which was shown to be due to the ability of the metabolite to cause microfilament disruption.

Recently, several other communesins have been isolated, including communesin C (**6**), D (**7**), E (**2**), F (**8**), G (**3**) and H (**4**).[3] These metabolites differ only in the substituents at N15 and N16, except for communesin F, which has a double bond instead of an epoxide at C21,22. Communesins C and D, along with communesin B, were isolated from a *Penicillium* species growing on the sponge *Axinella verrucosa*.[3a] All three compounds exhibit moderate antiproliferative activity against a series of leukemia cell lines. Communesins A, B, D, E and F were also isolated from the fermentation broth of okara (the insoluble residue of whole soybeans) with *Penicillium espansum* Link MK-57.[3b,4] These communesins show insecticidal activity against the third instar larvae of silkworms (LD_{50} = 150, 5, 80, 300 and 80 μg/g for communesins A, B, D, E and F, respectively). Communesins G and H, which were isolated from *Penicillium rivulum* Frisvad,[3c] were found to be inactive in antimicrobial, antiviral, and anticancer assays. Several additional communesin derivatives have recently been detected by mass spectrometry in a marine *Penicillium*, although the complete structures of these new metabolites have not yet been determined.[3d,5]

In 2002, Ireland et al. reported the isolation of a related metabolite, perophoramidine (**10**), from the tropical colonial ascidian *Perophora namei* collected in the Philippines.[6] Extensive spectroscopic analysis showed that the compound has a hexacyclic ring system (i.e. one less ring than the heptacyclic skeleton of the communesins due to the absence of the azepine-G-ring). Perophoramidine has bis-amidine rather than the bis-aminal functionality present in the communesins, as well as three halogen atoms in the aromatic rings. Perophoramidine also has adjacent quaternary carbons (C4, C20) similar to the communesins, but the relative stereochemistry of these two stereogenic centers was found to be opposite that of the communesins. The absolute stereochemistry of perophoramidine has not yet been established. Perophoramidine has cytotoxicity against the HCT116 colon carcinoma cell line (IC_{50} = 60 μM) due to induction of apoptosis by poly(adenosine-5′-diphosphateribose)polymerase (PARP) cleavage.

Although there is relatively little in the way of experimental evidence to date for the biogenesis of these metabolites, it is clear that they are derived from two tryptamines units, along with an isoprenoid moiety in the case of the communesins.[7] Structurally, the communesins and perophoramidine closely resemble members of the calycanthaceous family of plant alkaloids, whose biogenesis was suggested via an oxidative dimerization of tryptamine many years ago.[8] More recently, Stoltz, et al. have proposed an alternative pathway for formation of the communesins via a hetero Diels Alder step.[9]

The novel structures of the communesins and perophoramidine, as well as the promising biological activity of these alkaloids, have caught the attention of a number of synthetic chemists. To date, however, few successful total syntheses of these complex metabolites have been reported, perhaps due in part to difficulties in the stereoselective formation of the adjacent quaternary carbon centers. Funk and Fuchs made a breakthrough on these molecules by completing an elegant total synthesis of racemic perophoramidine utilizing a key biomimetically patterned hetero Diels-Alder reaction.[10] Unnatural dehaloperophoramidine has also been synthesized by Rainier and coworkers through a quite different strategy.[11] More recently, Qin, et al. have published the first total synthesis of racemic communesin F.[12] In

addition, a few other preliminary synthetic approaches to the core ring system of the communesins and perophoramidine have been reported.[13–15] Herein we report a new approach to the communesins, culminating in a total synthesis of racemic communesin F (**8**).[16,17]

Results and Discussion

Our initial unified approach to synthesis of both the communesins and perophoramidine was to rely on a tandem intramolecular Heck reaction/carbonylation of an acrylamide substrate such as **11** to form a lactam ester like **12** (Scheme 1). This compound would then be transformed to a tetracycle **13**, where the lactone carbonyl would become C9 of the communesins (C24 of perophoramidine) and provide a handle to establish the quaternary carbon at C8. In a series of publications, we have described the implementation of this basic strategy.[14] However, we have found that the success of the key Heck/carbonylation step was highly dependent upon the substituents in the two aromatic rings of **11**, and even in the optimal cases reproducibility often was an issue, particularly on large scale reactions. As a result, we decided to investigate a new strategy which would bypass this problematic step.

Thus, we considered the possibility of effecting a pivotal intramolecular Heck reaction[18] of a system such as **14** to form a tetracyclic enamine derivative **15** having the C7 quaternary carbon (Scheme 2). In this case, a carbonylation is not necessary since the tetrahydropiperidine ring incorporates a carbon which will become C9 of the communesins. Moreover, the cyclization product **15** has the enamine functionality in a position to facilitate introduction of the second (C8) quaternary center. It should be noted that we approached this transformation with some trepidation, since examples of intramolecular Heck reactions of tetrasubstituted double bonds are relatively uncommon.[19,20] In the work described below, we have investigated three series of Heck substrates **14** which differ in the substituent (X) at C12a in the F-ring. These substituents were intended to provide suitable functionality for eventual construction of the azepine-G-ring and also allow some flexibility with regard to protecting group compatibility during various steps in the synthesis.

In order to prepare the requisite substrates **14** for the Heck reaction, we employed the three different F-ring anilines shown in Scheme 3. Thus, known nitro benzyl alcohol **16**[21] was converted to the BOM ether **17a** and the TBS ether **17b** via standard procedures in good yields. The corresponding anilines **18a** and **18b** were then prepared conveniently by iron-promoted reduction of the nitro compounds. The third aniline required, **18c**, is a known compound which was accessed by the literature procedure.[22]

The B/C-ring component required for synthesis of the Heck substrates **14** was easily prepared from commercially available materials. Therefore, known enol triflate **19**,[23] readily accessible from the corresponding β-ketoester, was coupled in a Suzuki-Miyaura reaction with *o*-nitrobenzeneboronic acid to afford β-arylated-α,β-unsaturated ester **20** in excellent yield (Scheme 4).[24] This ester was converted to acid **21** by basic hydrolysis and then to the corresponding acid chloride **22**. Without purification, **22** was combined with anilines **18a–c** in the presence of Hunig's base to cleanly afford amides **23a–c**, respectively. It was found most convenient to replace the N-benzyl group of these intermediates at this point with a carbamate protecting group. Thus, exposure of **23a–c** to ethyl chloroformate in methylene chloride at room temperature resulted in high yields of ethyl carbamates **24a–c**.[25] All three compounds could be transformed to the N-methylamides **25a–c** in excellent yields with sodium hydride and methyl iodide.

With the requisite substrates in hand, we proceded to explore the key intramolecular Heck cyclizations. We were pleased to find that both O-protected hydroxymethyl-substituted systems **25a** and **25b** underwent rapid, high yielding Heck reactions under the conditions shown

in Scheme 4 to afford the desired spirocyclic enamides **26a** and **26b**, respectively. On the other hand, the cyclization of the C12a bromine-substituted substrate **25c** proved to be much more problematic.

Therefore, when compound **25c** was exposed to the same experimental conditions as used successfully for **25b**, a 1:1 mixture of the desired Heck product **26c** along with pentacyclic enamide **27** was formed in 74% total yield (Scheme 5). The latter compound presumably arises from a subsequent Heck arylation of bromide **26c**. However, after some experimentation, it was found that by lowering the reaction temperature to 100 °C, and allowing the reaction to proceed for one hour produced a mixture of **26c** and **27** in a 6.7:1 ratio in 51% total yield, along with 40% of recovered starting material **25c** which could be recycled. Since compounds **26c** and **27** were not easily separable by silica gel chromatography, the crude mixture was reduced with iron/concentrated HCl to afford aniline **28** which could then be separated from the amine derived from **27** (84% isolated yield based on the amount of nitro compound **26c** in the mixture). This material was next converted to the Boc derivative **29c** in high yield.

The nitro groups of the two other Heck products **26a** and **26b** were also converted to the corresponding amines, although each required a different reduction procedure. The BOM-protected system **26a** was reduced by catalytic hydrogenation at 40 atm using 5% Pt/C to afford the corresponding unstable aniline (without BOM hydrogenolysis), which was immediately transformed to the Boc derivative **29a** in 87% yield for the two steps (Scheme 6). In the case of the TBS-protected compound **26b**, catalytic hydrogenation was best effected using 10% Pd/C at 1 atm, followed by Boc protection to produce carbamate **29b** in 85% overall yield.[26]

The next objective in the synthesis was to construct the southern aminal functionality and the attendant D-ring of the communesins via a partial reduction of the lactam functionality of our three intermediates. After screening several hydride reagents,[27] it was discovered that alane-dimethylethylamine complex effected lactam reduction/cyclization of **29a–c** in one operation to directly generate the desired pentacyclic Boc-protected aminals **30a–c** in good yields.

At this stage, we turned to introduction of the quaternary carbon at C8 with the desired stereochemistry, along with subsequently forming the upper aminal moiety. Initial studies were carried out with the TBS-protected enamide **30b**, which was treated with an excess of butyllithium at low temperature, followed by addition of allyl iodide to afford the desired C-allylated imine **32** as the major product along with a small amount of the N-allyl enamine **33** (Scheme 7). Reaction of the enamide **30b** with the alkyllithium reagent undoubtedly produces the intermediate lithio enamine **31**,[28] which undergoes alkylation from the less congested convex face to form **32** having the required vicinal quaternary carbon stereochemistry of the communesins. The structure and stereochemistry of this intermediate were confirmed by HMQC, HMBC and NOESY-NMR experiments. It might also be noted that we have been unable to alkylate **31** and related systems (Cf. **40**, **50**) with any two carbon electrophiles such as nitroethylene, ethyl iodoacetate, iodoacetonitrile, 2-iodoethylazide, *N*-nosylaziridine, ethylene oxide, etc.[17] In addition, all attempted cyclopropanations of the enamide also failed.[29,30]

Since it seemed possible that the C-allylation product **32** could arise via an aza-Cope rearrangement from the N-allyl compound **33**, we briefly probed this possibility in a related series where the TBS group of **32** and **33** had been replaced by a *p*-methoxyphenyl (PMP) protecting group.[17a] Thus, both allyl pentacycles were first reexposed to the allylation conditions, but no change was detected. In refluxing toluene (bp 110 °C) both compounds were stable and no isomerization occurred. At a higher temperature in refluxing *o*-xylene (bp 143–145 °C), the N-allyl pentacycle began to decompose but none of the C-allyl compound was detected. However, at this same temperature the C-allyl pentacycle was slowly converted to

the N-allyl product, and after heating for 17 hours, the ratio of C-allyl/N-allyl compounds in the mixture was found to be 1:0.6. This unexpected conversion can be rationalized by invoking a 1-aza-Cope rearrangement, which is usually unfavorable relative to its counterpart, a 3-aza-Cope rearrangement. However, in this specific system, relief of ring strain or of unfavorable steric interactions could be the driving force for the 1-aza-Cope rearrangement.[31]

With intermediate imine **32** now in hand, our plan for completion of the synthesis was to next construct the northern aminal functionality of the metabolites containing the A/B-ring system, and then finally establish the azepine-G-ring. Towards this end, it was necessary to oxidatively cleave the allyl group, although this transformation could not be directly effected on **32** due to the presence of the imine functionality. In an attempt to protect the imine, compound **32** was treated with diethyl pyrocarbonate in EtOH,[32] which provided the desired α-ethoxycarbamate **34** as a mixture of diastereomers, but to our surprise a significant amount of aldehyde **35** was also produced (Scheme 8). The N,O acetal **34** was also found to be rather sensitive to handling and tended to rearrange to **35**. Formation of this aldehyde can be rationalized as occurring via an intermediate N-acyliminium ion generated from the imine **32** and ethyl pyrocarbonate. As can be seen from models, there is a close proximity between the siloxymethyl group at C12a and the electrophilic N-acyliminium ion functionality which facilitates an intramolecular hydride transfer.[33] In an attempt to decrease the amount of **35** formed from the imine, the reaction conditions were varied, but neither low temperature (−78 °C) nor addition of bases (NEt_3, K_2CO_3) caused any significant improvement. It might also be noted that the PMP-protected variant of silyl ether **32** was even more prone to undergo this hydride migration.

We therefore decided to explore manipulating the terminal olefin moiety of the crude **34**/**35** product mixture. It was found that by three sequential reactions (i.e. dihydroxylation, oxidative cleavage and reduction), the desired alcohol **36** could be obtained by chromatography as a 2:1 mixture of diastereomers in 45% yield based on imine **32**, along with diol **37** in 30% yield, which is derived from aldehyde **35**.

In an attempt to continue the synthesis, alcohol **36** was first converted to the corresponding azide under Mitsunobu conditions (Scheme 9). This azide was then reduced by catalytic hydrogenation and the resulting amine was protected in a one-pot reaction to afford N-Boc compound **38**. Unfortunately, we were unable to cyclize **38** to the desired northern aminal **39**, but rather under acidic conditions only a rearranged aldehyde was observed which results via a hydride migration from the C11 methylene group.

Since the primary difficulty with the sequence involving the siloxymethyl series of compounds was due to the undesired hydride migrations outlined above, we decided to eliminate any possibility of this rearrangement by replacement of the C12a carbon substituent with a bromine. It might also be noted that a bromine substituent was used as a C12a functional handle to construct the azepine-G-ring in Qin's total synthesis of communesin F.[12b] We therefore returned to brominated tetracyclic enamide **30c**. Conversion of this compound to the corresponding lithio enamine using the butyllithium procedure described above (Cf. Scheme 7) was problematic since some halogen-metal exchange occurred under these conditions. However, the enamide could be tranformed by basic hydrolysis to the unstable NH enamine **40**, which without purification was treated with LDA and allyl iodide to form the C-allyl imine **41** in 58% isolated yield along with 29% of the corresponding N-allyl enamine.

With alkylated pentacycle **41** in hand, we subsequently investigated the oxidative cleavage of the allyl group. As we had hoped, exposure of imine **41** to diethyl pyrocarbonate in ethanol cleanly produced α-ethoxycarbamate **42** (Scheme 10). However, much to our surprise dihydroxylation of **42** followed by oxidative cleavage with periodate gave hexacyclic acetal **43** (42% overall yield for three steps from **41**) as a mixture of epimers instead of the desired

aldehyde. The structure of the cyclic acetal **43** was confirmed by 2D NMR studies (HMQC, HMBC, and NOESY). Cyclic acetal **43** could then be hydrolyzed with aqueous acid to the hemiacetal **44** in good yield. With the hope that there might be some aldehyde in equilibrium with this hemiacetal, attempts were made at reductive aminations of **44**, but to no avail. In view of these problems in forming the northern aminal, along with some of the poor reaction yields observed in the C12a bromine series of intermediates, the synthetic strategy was revised again.

Because the many problems encountered in attempting to form the upper aminal primarily involved an imine, it was decided to avoid such functionality and instead utilize a B-ring lactam. Moreover, we elected to adopt an approach analogous to that of Qin,[12b] where the azepine-G-ring was positioned prior to forming the A/B-ring northern aminal. To investigate this new strategy, enamide **30a** in the BOM-protected series was first hydrolyzed to the unstable NH enamine **45**, which without purification was treated with cyanogen azide at room temperature to afford the N-cyanoamidine **47** (Scheme 11).[34] This transformation is believed to occur via an initial [3+2]-dipolar cycloaddition of the enamine to afford triazole **46**, which then rearranges with concomitant loss of nitrogen to form product **47**. It was then found that basic hydrolysis of this amidine gave the lactam **48** as a single stereoisomer. Subsequent base mediated N-acylation of lactam **48** led to N-Boc lactam **49**, but also caused isomerization to a 3:1 mixture of epimers at C8, which was of no consequence to the synthesis.

Gratifyingly, alkylation of the mixture of N-Boc lactams **49** could be effected with potassium *t*-butoxide and allyl iodide to afford the desired product **51** as a single C8 stereoisomer in excellent yield. This alkylation proceeds via attack of the iodide on the N-Boc lactam enolate **50** from the least congested convex face, analogous to the stereoselective alkylations of the lithio enamines done previously (*vide supra*). To continue the synthesis it was found best to selectively remove the Boc group on the lactam at this point by basic cleavage to produce **52**.

In a straightforward series of reactions, the allyl group of **52** was oxidatively cleaved to the aldehyde which without purification was reduced to the corresponding alcohol. This alcohol could then be transformed into the mesylate **53** in good overall yield for the three steps (Scheme 12). Removal of the BOM group of **53** was effected by hydrogenolysis with Pearlman's catalyst and the resulting benzyl alcohol was immediately oxidized with the Dess-Martin periodinane to produce aldehyde **54**. Displacement of the mesylate with sodium azide in DMF afforded azido aldehyde **55**.

We next investigated homologation of this compound to the α,β-unsaturated ketone **56**, but to our surprise the aldehyde was found to be unreactive in Wadsworth-Emmons-Horner or Wittig condensations, perhaps for steric reasons. However, it was discovered that aldehyde **55** underwent a clean cross aldol reaction with acetone in the presence of aqueous sodium hydroxide to produce the desired (*E*)-unsaturated ketone **56** in excellent yield. In order to activate the δ-lactam for rearrangement in the next step, a Boc group was installed to form **57**. With enone **57** in hand, our initial plan was to effect a one-pot tandem azide reduction, lactam opening and subsequent aza-Michael addition of the resulting N-Boc carbamate to the α,β-unsaturated ketone moiety to sequentially form the A-ring and the azepine-G-ring. Therefore, N-Boc-lactam azide **57** was reduced with trimethylphosphine in THF/water which led to the γ-lactam **58** in good yield, but this procedure did not promote the desired conjugate addition to the enone. All attempts to subsequently effect an aza-Michael addition of the N-Boc carbamate in **58** to the α,β-unsaturated ketone moiety to form the azepine ring under a variety of acidic or basic conditions unfortunately also failed.

We therefore decided to generate the azepine ring of communesin F using the strategy of Qin, et al.[12a,35] Thus, exposure of ketone **58** to methyllithium in THF at low temperature led to the

(*E*)-allylic alcohol **59** in 73% yield (Scheme 13). Subsequent treatment of this alcohol with PPTS at room temperature promoted a stereoselective allylic substitution reaction which produced the hexacyclic G-ring product **61** having the communesin configuration at C11 in 62% isolated yield. In addition, a 24% yield of the diene **60** resulting from dehydration of starting alcohol **59** was formed, similar to what was observed in the Qin system. The stereochemical outcome of this cyclization is not surprising since inspection of models indicates that the conformation shown in **59** is preferred in order to minimize steric interactions with the γ-lactam Bring. Thus, an acid catalyzed allylic substitution by the N-Boc group via this conformation produces the requisite communesin configuration at C11 in **61**.

To complete the total synthesis, it was now necessary to form the northern aminal. Towards this end, γ-lactam **61** was treated with commercially available triethyloxonium fluoroborate and DIEA in methylene chloride in order to form the corresponding ethyl imidate, similar to the conditions reported by Qin et al.[12b] Although this reaction produced some of the desired compound, a substantial amount of an unidentified byproduct was formed. Alternatively, the use of trimethyloxonium fluoroborate in the presence of Hunig's base cleanly generated the desired methyl imidate **62**.

Since the upper Boc protecting group proved to be much more labile towards acid than the one on the southern aminal, it could be selectively removed with 5% trifluoroacetic acid in methylene chloride. Upon neutralization of the resulting amine TFA salt with aqueous sodium bicarbonate, cyclization occurred spontaneously to form the heptacyclic amidine **63**.[36] Reduction of this amidine with sodium borohydride in acetic acid containing acetic anhydride occurred stereoselectively from the less hindered face to give the N-acetyl aminal **64**. Finally, removal of the Boc protecting group on the lower aminal could then be effected with 40% TFA in methylene chloride to afford racemic communesin F (**8**). This material, which exists as a 2.6:1 mixture of acetamide rotamers in $CDCl_3$, had proton and carbon NMR spectral data identical to that reported by the Qin group for the alkaloid.[12b]

In conclusion, we have achieved a stereoselective total synthesis of the heptacyclic fungal alkaloid (±)-communesin F (**8**) in about 30 steps from readily prepared enol triflate **19** and commercially available *o*-nitrobenzeneboronic acid. Notable reactions in the sequence include a rare example of an intramolecular Heck cyclization of a tetrasubstituted alkene to generate a spiro-tetracycle with the C7 quaternary carbon center of the metabolite, a one-pot reductive cyclization of an N-Boc aniline onto an oxindole moiety to form a pentacyclic system incorporating the southern aminal, a stereoselective N-Boc-lactam enolate C-allylation to introduce the C8 quaternary carbon center, and an azide reduction/*N*-Boc-δ-lactam opening cascade eventually leading to the northern aminal. In principle, it should be possible to effect the key intramolecular Heck reaction of substrate **25a** enantioselectively to ultimately produce the natural (−)-enantiomer of communesin F.[37] We hope to explore this transformation in future work.

Experimental Section

Synthesis of BOM Ether 17a

To a solution of (2-iodo-3-nitrophenyl)methanol[21] (**16**, 263 mg, 0.94 mmol) in THF (5.0 mL) was added TBAI (70 mg, 0.19 mmol), DIPEA (0.25 mL, 1.41 mmol) and BOMCl (0.13 mL, 0.94 mmol). The reaction mixture was heated at 70 °C for 14 h and quenched by the addition of saturated aqueous $NaHCO_3$. The solution was then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/4) to give the BOM ether **17a** (232 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.58 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.45-7.32 (m, 5H), 4.98 (s, 2H), 4.74 (s, 2H), 4.72 (s, 2H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 154.7, 143.8, 137.4, 131.0, 128.8, 128.4, 127.8, 127.7, 123.3, 94.4, 88.7, 73.9, 69.9; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{15}NO_4I$, 400.0046; found, 400.0039.

Synthesis of Aniline 18a

To a solution of nitro compound **17a** (3.16 g, 7.92 mmol) in EtOH (50.0 mL) was added iron powder (2.21 g, 39.59 mmol) and AcOH (6.8 mL). The reaction mixture was heated at 60 °C for 12 h and then cooled to rt. The mixture was filtered and the filtrate was concentrated. The residue was diluted with EtOAc and H_2O and basified with solid Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1) to provide the iodoaniline **18a** (2.22 g, 76%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.31 (m, 5H), 7.16 (br m, 1H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.77 (br s, 1H), 4.94 (s, 2H), 4.74 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 141.0, 137.7, 128.8, 128.4, 127.9, 127.6, 119.2, 114.3, 94.2, 88.4, 74.2, 69.6; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{17}NO_2I$, 370.0304; found, 370.0295.

Synthesis of Ester 20

To a solution of enol triflate **19**[23] (763 mg, 1.94 mmol) and *o*-nitrobenzeneboronic acid (356 mg, 2.13 mmol) in DME (11.0 mL) and water (3.7 mL) were added $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) and Na_2CO_3 (617 mg, 5.82 mmol). The reaction mixture was stirred at 80 °C for 1 h and then cooled to rt. The solution was diluted with H_2O and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/3) to give arylated compound **20** (697 mg, 98%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.57 (ddd, *J* = 0.8, 7.6, 7.6 Hz, 1H), 7.46-7.39 (m, 3H), 7.36-7.26 (m, 3H), 7.19 (dd, *J* = 1.3, 7.6 Hz, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 3.73 (q, *J* =12.7 Hz, 2H), 3.48, 3.22 (ABq, *J* = 17.9 Hz, 2H), 2.83 (t, *J* = 5.8 Hz, 2H), 2.60 (m, 2H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.3, 144.7, 138.2, 137.1, 133.5, 130.1, 129.4, 128.8, 128.4, 127.7, 125.1, 124.6, 61. 8, 60.7, 58.6, 49.2, 26.0, 14.0; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_4$, 367.1658; found, 367.1651.

Synthesis Carboxylic Acid 21

To a solution of ester **20** (18.23 g, 49.75 mmol) in MeOH (260 mL) and water (108 mL) was added $LiOH{\cdot}H_2O$ (10.45 g, 249.05 mmol). The reaction mixture was stirred at 50 °C for 12 h before MeOH was removed under reduced pressure. The resulting aqueous solution was acidified with 1 N HCl to pH 5–6 and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1/10) to give the carboxylic acid **21** (16.48 g, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ 12.6 (br s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.1 Hz, 1H), 7.33-7.26 (m, 6H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.03-3.90 (m, 2H), 3.73-3.51 (m, 2H), 3.00 (br s, 1H), 2.78 (br s, 1H), 2.47 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 148.5, 136.6, 135.6, 133.8, 131.8, 130.9, 130.7, 129.4, 129.3, 128.7, 127.3, 124.2, 58.6, 54.5, 46.6, 23.3; HRMS-ES (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_4$, 339.1345; found, 339.1325.

Synthesis of Amide 23a

The acid **21** (11.33 g, 38.49 mmol) was dissolved in $SOCl_2$ (25.0 mL) and the solution was refluxed for 3 h. Excess $SOCl_2$ was distilled off and the resulting residue was dried under high vacuum and then dissolved in CH_2Cl_2 (30.0 mL). To a stirred solution of aniline **18a** (9.16 g, 24.80 mmol) and DIPEA (17.3 mL, 99.31 mmol) in CH_2Cl_2 (50.0 mL) was added the above acid chloride **22** solution dropwise at rt. The reaction mixture was further stirred at rt for 12 h,

and was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3) to give the amide **23a** (14.88 g, 87% based on aniline **18a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.85 (s, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47-7.31 (m, 12H), 7.28-7.18 (m, 2H), 4.91 (s, 2H), 4.70 (s, 2H), 4.63 (s, 2H), 3.76 (br d, *J* = 5.5 Hz, 2H), 3.36, 3.14 (ABq, *J* = 16.9 Hz, 2H), 2.97-2.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 147.6, 140.7, 137.9, 137.4, 137.3, 134.8, 133.5, 130.6, 129.3, 128.65, 128.59, 128.3, 128.13, 128.09, 127.6, 127.4, 127.0, 124.8, 124.4, 121.4, 94.01, 93.94, 73.9, 69.4, 61.1, 56.6, 48.5, 26.2; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{34}H_{33}N_3O_5I$, 690.1465; found, 690.1472.

Synthesis of Ethyl Carbamate 24a

To a stirred solution of amide **23a** (3.13 g, 4.54 mmol) in CH_2Cl_2 (35.0 mL) was added $ClCO_2Et$ (0.52 mL, 5.45 mmol) dropwise at 0 °C. After the addition was complete, the ice bath was removed and the mixture was stirred at rt for 12 h before saturated aqueous $NaHCO_3$ was added. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc/CH_2Cl_2, 5/3/2) to provide carbamate **24a** (2.92 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.81 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.73 (s, 1H), 7.63-7.58 (m, 1H), 7.47-7.27 (m, 7H), 7.24-7.14 (m, 2H), 4.86 (s, 2H), 4.65 (s, 2H), 4.58 (s, 2H), 4.41- 4.09 (br m, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.87-3.75 (br m, 2H), 2.85-2.68 (br m, 2H), 1.45-1.29 (br m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 154.9, 147.6, 140.8, 137.7, 137.3, 133.8, 133.6, 130.7, 129.1, 128.4, 128.2, 127.6, 127.5, 125.1, 124.7, 121.5, 94.3, 94.0, 73.9, 69.4, 61.4, 47.1, 39.5, 25.8, 14.4; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{30}H_{31}N_3O_7I$, 672.1207; found, 672.1226.

Synthesis of N-Methyl Amide 25a

To a suspension of NaH (192 mg, 60% dispersion in mineral oil, 4.79 mmol) in THF (10.0 mL) was added a solution of amide **24a** (2.92 g, 4.35 mmol) in THF (30.0 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and MeI (0.33 mL, 5.22 mmol) was added at this temperature. The reaction mixture was warmed to rt and stirred for 12 h before the addition of saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 3/2) to provide N-methyl amide **25a** (2.74 g, 92%). ^{1}H NMR (300 MHz, CD_3CN) δ 8.07 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.76-7.73 (m, 1H), 7.62-7.56 (m, 1.7H), 7.47-7.44 (br m, 1H), 7.40-7.29 (m, 6H), 7.02 (br s, 0.3H), 6.40 (br s, 0.3H), 4.93 (s, 0.7H), 4.87 (s, 1.3H), 4.69 (s, 1H), 4.64 (s, 1.3H), 4.59 (s, 1.3H), 4.40 (br s, 1H), 4.20 (q, *J* = 7.1 Hz, 1.5H), 4.11-4.00 (m, 1H), 3.86-3.72 (m, 1.3H), 3.45 (br s, 0.3H), 3.11 (s, 2H), 2.99 (s, 0.3H), 2.92 (s, 0.8H), 2.87 (s, 0.3H), 2.58 (s, 1.3H), 2.26 (s, 0.6H), 1.30 (t, *J* = 6.9 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_3CN, 65 °C) δ 170.0, 156.6, 150.2, 147.0, 144.2, 139.7, 134.9, 134.2, 133.3, 132.0, 130.7, 130.6, 129.6, 129.3, 129.1, 128.8, 128.6, 126.1, 125.6, 103.1, 96.0, 75.3, 71.0, 62.5, 49.0, 48.1, 41.1, 39.0, 37.7, 27.2, 15.3; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{31}H_{33}N_3O_7I$, 686.1363; found, 686.1371.

Synthesis of Tetracyclic Enamide 26a

To a solution of N-methyl amide **25a** (2.21 g, 3.23 mmol) in DMA (56.0 mL) were added $Pd(OAc)_2$ (145 mg, 0.65 mmol), PPh_3 (339 mg, 1.29 mmol), *n*-Bu_4NBr (2.08 g, 6.45 mmol) and K_2CO_3 (892 mg, 6.48 mmol). The mixture was stirred at 150 °C for 25 min, then cooled to rt and was diluted with H_2O. The aqueous solution was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash

column chromatography on silica gel (hexanes/EtOAc, 1/2) to provide spirocyclic enamide **26a** (1.88 g, 90%). ^{1}H NMR (300 MHz, CD_3CN, 65 °C) δ 7.53-7.49 (m, 2H), 7.40-7.30 (m, 6H), 7.28-7.21 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.80-6.84 (m, 2H), 4.85-4.80 (m, 2H), 4.36 (d, *J* = 11.9 Hz, 1H), 4.31, 4.26 (ABq, *J* = 7.1 Hz, 2H), 4.07-3.99 (m, 2H), 3.23 (s, 3H), 2.64-2.53 (m, 1H), 1.98-1.89 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN, 65 °C) δ 178.8, 154.5, 150.9, 145.2, 139.7, 136.3, 132.6, 132.4, 132.15, 132.11, 130.1, 129.6, 129.4, 129.0, 128.8, 125.2, 124.9, 110.4, 109.1, 95.8, 70.9, 66.7, 63.8, 50.5, 38.9, 31.5, 27.5, 15.0; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{31}H_{32}N_3O_7$, 558.2240; found, 558.2238.

Synthesis of N-Boc Aniline 29a

To a beaker containing a solution of the Heck product **26a** (1.71 g, 3.07 mmol) in toluene (30.0 mL) was added 5% platinum on carbon (514 mg). The beaker was then transferred into a high-pressure reaction vessel and flushed with H_2. The hydrogen pressure was increased to 40 atm, and the reaction mixture was stirred at rt for 14 h. The pressure was released and the suspension was filtered through a pad of Celite. The solvent was removed to give the aniline which decomposed on standing and therefore was used immediately in crude form.

To a solution of the freshly prepared crude aniline in THF (90.0 mL) and H_2O (30.0 mL) were added K_2CO_3 (8.49 g, 61.43 mmol) and $(Boc)_2O$ (10.05 g, 46.05 mmol). The mixture was stirred at 60 °C for 20 h. The aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/4) to provide N-Boc aniline **29a** (1.68 g, 87% for 2 steps). ^{1}H NMR (300 MHz, CD_3CN, 65 °C) δ 7.72 (d, *J* = 8.9 Hz, 1H), 7.43-7.26 (m, 7H), 7.21 (s, 1H), 7.15-7.08 (m, 2H), 6.80-6.71 (m, 3H), 4.94, 4.91 (ABq, *J* = 6.7 Hz, 2H), 4.82, 4.73 (ABq, *J* = 11.6 Hz, 2H), 4.70 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.17-4.01 (m, 2H), 3.11 (s, 3H), 2.60-2.48 (m, 1H), 2.10-1.99 (m, 1H), 1.55 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN, 65 °C) δ 180.1, 154.7, 154.5, 145.1, 139.6, 138.6, 136.1, 131.8, 131.7, 129.99, 129.94, 129.6, 129.1, 129.0, 128.8, 125.1, 123.7, 122.9, 112.0, 109.2, 96.1, 80.9, 71.1, 67.0, 63.5, 51.8, 39.3, 32.1, 29.0, 27.4, 15.1; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{42}N_3O_7$, 628.3023; found, 628.3022.

Synthesis of Pentacyclic Aminal 30a

To a solution of N-Boc aniline **29a** (302 mg, 0.48 mmol) in THF (15.0 mL) was added $AlH_3{\cdot}Me_2NEt$ (1.44 mL, 0.5 M in toluene, 0.72 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred at rt for 4 h before saturated aqueous Na_2SO_4 was added. The aqueous mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/9) to give the aminal **30a** (250 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 6H), 7.19 (dd, *J* = 1.4, 7.3 Hz, 2H), 7.05 (br m, 1H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.56 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 7.8 Hz, 1H), 5.82 (s, 1H), 4.84 (s, 2H), 4.74-4.65 (m, 3H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.31-4.15 (m, 3H), 3.51 (br s, 1H), 3.00 (s, 3H), 2.50-2.35 (m, 2H), 1.53 (s, 9H), 7.1 (t, *J* = 1.35 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN, 65 °C) δ 154.3, 154.0, 151.8, 139.2,139.0, 134.4, 134.1, 130.4, 128.83, 128.76, 128.2, 127.9, 126.8, 125.7, 125.1, 124.5, 118.7, 116.8, 104.9, 94.9, 85.6, 81.5, 69.9, 65.5, 62.6, 52.0, 40.5, 34.6, 30.5, 28.0, 14.3; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{42}N_3O_6$, 612.3074; found, 612.3055.

Preparation of Cyanogen Azide

To a solution of cyanogen bromide (536 mg, 5.06 mmol) in CH_3CN (10.0 mL) was added NaN_3 (339 mg, 5.22 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h to give a solution of NCN_3 in CH_3CN (0.50 M) which can be stored at 0 °C for several weeks without noticeable decomposition.

Synthesis of N-Cyanoamidine 47

To a solution of enamide **30a** (202 mg, 0.33 mmol) in EtOH (10.0 mL) was added 1 N aqueous KOH solution (10.0 mL, 10.0 mmol). The mixture was stirred at 94 °C for 3 h and then cooled to rt. After removal of EtOH *in vacuo*, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Since the resulting enamine **45** was unstable and decomposed during chromatographic purification, the material was used directly in the next step.

To a solution of the crude enamine in MeCN (15.0 mL) was added NCN_3 (1.0 mL, 0.5 M in MeCN, 0.50 mmol, freshly prepared). The solution was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 2/3) to give the N-cyanoamidine **47** (178 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 7.44-7.29 (m, 5H), 7.20 (d, *J* = 3.0 Hz, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.06-7.00 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.09 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 4.92, 4.89 (ABq, *J* = 6.9 Hz, 2H), 4.81, 4.63 (ABq, *J* = 11.7 Hz, 2H), 4.74 (s, 2H), 4.34 (s, 1H), 3.87-3.84 (m, 1H), 3.55-3.51 (m, 1H), 2.78 (s, 3H), 2.75-2.64 (m, 1H), 2.12 (dd, *J* = 3.5, 14.3 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 150.1, 150.6, 137.5, 136.4, 132.8, 132.3, 129.8, 129.1, 128.5, 127.8, 127.6, 127.5, 125.9, 125.7, 119.5, 116.3, 104.5, 93.3, 81.6, 78.8, 69.8, 65.9, 53.9, 46.8, 39.1, 30.5, 29.9, 28.1; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{34}H_{38}N_5O_4$, 580.2924; found, 580.2918.

Synthesis of Lactam 48

To a solution of N-cyanoamidine **47** (178 mg, 0.33 mmol) in EtOH (15.0 mL) was added 1 N aqueous KOH solution (15.0 mL, 15.0 mmol). The mixture was stirred at 94 °C for 12 h and then cooled to rt. After removal of EtOH *in vacuo*, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the lactam **48** (102 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H), 7.19-7.16 (m, 3H), 7.05-6.95 (m, 2H), 6.58 (d, *J* = 7.6 Hz, 1H), 6.44 (br s, 1H), 6.13 (s, 1H), 6.09 (d, *J* = 7.9 Hz, 1H), 4.92, 4.89 (ABq, *J* = 6.9 Hz, 2H), 4.83, 4.72 (ABq, *J* = 11.6 Hz, 2H), 4.78 (s, 2H), 4.17 (s, 1H), 3.86 (t, *J* = 11.7 Hz, 1H), 3.39-3.35 (m, 1H), 2.79 (s, 3H), 2.75-2.69 (m, 1H), 2.08-2.01 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 153.4, 150.5, 137.6, 136.3, 132.8, 132.5, 129.9, 128.7, 128.4, 128.3, 127.7, 127.6, 127.2, 125.6, 119.1, 104.3, 93.4, 81.1, 79.1, 69.6, 65.7, 54.6, 49.1, 38.2, 31.5, 30.0, 28.1; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{33}H_{38}N_3O_5$, 556.2811; found, 556.2820.

Synthesis of N-Boc Lactams 49

To a solution of lactam **48** (343 mg, 0.62 mmol) in THF (15.0 mL) was added LiHMDS (0.93 mL, 1.0 M in THF, 0.93 mmol). The mixture was stirred at rt for 10 min and $(Boc)_2O$ (141 mg, 0.65 mmol) was added. The reaction mixture was stirred at rt for another 10 min and quenched with aqueous saturated $NaHCO_3$. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3) to give the *N*-Boc lactam (384 mg, 95%) as a 1:3 mixture of epimers **49a** and **49b**. For analytical purposes, the N-Boc lactam mixture was carefully purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1 then 7/3) to give pure samples of **49a** and **49b**.

49a—^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.7 Hz, 1H), 7.44-7.37 (m, 4H), 7.35-7.31 (m, 1H), 7.02-6.98 (m, 3H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H), 6.20 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 4.84, 4.80 (ABq, *J* = 6.8 Hz, 2H), 4.69, 4.61 (ABq, *J* = 12.0 Hz, 2H), 4.50, 4.42 (ABq, *J* = 11.7 Hz, 2H), 4.36-4.33 (m, 1H), 3.87 (s, 1H), 3.83-3.77 (m, 1H), 2.97 (s, 3H), 2.52-2.37 (m, 2H), 1.60 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4,

154.2, 152.1, 151.4, 138.1, 137.8, 133.0, 130.6, 128.6, 128.4, 128.3, 128.1, 127.8, 127.5, 126.1, 125.8, 125.2, 119.4, 105.2, 93.7, 84.9, 83.3, 81.2, 69.2, 66.8, 56.6, 45.2, 42.7, 34.5, 30.7, 28.1, 28.0; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{46}N_3O_7$, 656.3336; found, 656.3320.

49b—^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 4H), 7.35-7.32 (m, 1H), 7.28 (br s, 1H), 7.19-7.12 (m, 2H), 7.03-6.94 (m, 2H), 6.56 (d, *J* = 5.7 Hz, 1H), 6.10 (s, 1H), 6.09 (d, *J* = 5.9 Hz, 1H), 4.91, 4.88 (ABq, *J* = 5.1 Hz, 2H), 4.82, 4.69 (ABq, *J* = 8.8 Hz, 2H), 4.73 (d, *J* = 1.4 Hz, 2H), 4.35 (s, 1H), 4.10-4.04 (m, 1H), 3.96-3.93 (m, 1H), 2.84-2.76 (m, 1H), 2.78 (s, 3H), 2.17 (d, *J* = 10.6 Hz, 1H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 152.8, 150.4, 137.5, 136.2, 132.6, 132.1, 129.7, 128.7, 128.3, 128.0, 127.63, 127.57, 127.3, 125.7, 125.5, 119.2, 104.4, 93.2, 82.8, 81.2, 79.7, 69.6, 65.7, 55.2, 51.6, 42.2, 32.3, 29.9, 28.0, 27.7; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{38}H_{46}N_3O_7$, 656.3336; found, 656.3344.

Synthesis of C-Allyl Lactam 51

To a solution of N-Boc lactams **49** (207 mg, 0.32 mmol) in THF (20.0 mL) was added a solution of KO*t*-Bu (42 mg, 0.38 mmol) in THF (1.5 mL) dropwise at −78 °C, followed immediately by the addition of allyl iodide (0.48 mL, 1.0 M in THF, 0.48 mmol). The dry ice-acetone bath was removed and the mixture was warmed to rt and stirred for 40 min before aqueous saturated $NaHCO_3$ was added. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1 then 7/3) to give the C-allyl lactam **51** (191 mg, 87%). ^{1}H NMR (300 MHz, CD_3CN, 65 °C) δ 8.31 (dd, *J* = 1.6, 7.7 Hz, 0.8H), 7.44-7.31 (m, 10H), 7.24(d, *J* = 9.0 Hz, 1H), 7.10-7.03 (m, 2H), 6.98-6.88 (m, 5H), 6.53 (d, *J* = 7.9 Hz, 1.8H), 6.36 (dd, *J* = 1.0, 7.8 Hz, 0.8H), 6.21 (d, *J* = 7.8 Hz, 1H), 5.75 (s, 1H), 5.70 (s, 1H), 5.64-5.55 (m, 1.8H), 5.13-5.03 (m, 2H), 4.93-4.83 (m, 4H), 4.80-4.75 (m, 2H), 4.67-4.52 (m, 5.8H), 4.35-4.17 (m, 4.8H), 3.84-3.77 (m, 0.8H), 3.73-3.62 (m, 0.8H), 3.13-3.02 (m, 1.7H), 3.00 (s, 2.8H), 2.93 (s, 3H), 2.91-2.84 (m, 1H), 2.70 (td, *J* = 5.7, 13.7 Hz, 1H), 2.26 (s, 2.3H), 2.25-2.12 (m, 2H), 1.93-1.88 (m, 1H), 1.58 (s, 9H), 1.55 (s, 9H), 1.51 (s, 15H); ^{13}C NMR (75 MHz, CD_3CN, 65 °C) δ 173.0, 155.3, 155.2, 155.1, 154.4, 152.6, 152.3, 146.4, 140.3, 139.9, 139.8, 139.6, 135.4, 135.3, 134.8, 134.4, 130.7, 130.4, 130.0, 129.7, 129.6, 129.5, 129.1, 128.8, 128.7, 128.6, 127.6, 127.4, 127.3, 125.9, 125.2, 120.3, 118.8, 118.7, 118.4, 107.4, 106.2, 105.3, 96.0, 95.8, 86.5, 84.6, 84.0, 82.8, 82.6, 82.1, 70.94, 70.88, 70.7, 68.1, 66.1, 60.8, 55.9, 52.4, 45.1, 40.7, 37.4, 32.1, 31.1, 30.9, 28.92, 28.89, 28.8, 28.7; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{41}H_{50}N_3O_7$, 696.3649; found, 696.3651.

Synthesis of NH-Lactam 52

To a solution of the N-Boc lactam **51** (191 mg, 0.27 mmol) in EtOH (28.0 mL) was added 1 N aqueous KOH solution (2.8 mL, 2.8 mmol). The mixture was stirred at 80 °C for 13 h and then cooled to rt. After removal of EtOH *in vacuo*, the cloudy aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7/3 then 1/1) to give the NH-lactam **52** (155 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27-8.22 (m, 1H), 7.40-7.24 (m, 5H), 6.97-6.82 (m, 4H), 6.53 (dd, *J* =0.8, 7.8 Hz, 1H), 6.26 (dd, *J* = 0.9, 7.8 Hz, 1H), 6.25 (s, 1H), 5.88-5.74 (m, 1H), 5.63 (s, 1H), 4.88-4.81 (m, 2H), 4.84, 4.77 (ABq, *J* = 6.7 Hz, 2H), 4.70, 4.61 (ABq, *J* = 11.9 Hz, 2H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.24 (d, *J* = 12.1 Hz, 1H), 3.49 (td, *J* = 4.5, 12.8 Hz, 1H), 3.25-3.18 (m, 1H), 2.97 (s, 3H), 2.85 (d, *J* = 7.0 Hz, 2H), 2.54 (td, *J* = 6.0, 13.4 Hz, 1H), 1.95 (dd, *J* = 4.2, 13.5 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 154.1, 150.8, 138.5, 137.8, 134.4, 133.8, 132.7, 128.8, 128.4, 128.3, 127.8, 127.6, 126.8, 126.3, 125.9, 124.0, 119.4, 116.9, 106.1, 94.2, 83.1, 81.2, 69.6, 66.6, 58.6, 48.7, 40.6, 39.3, 31.4, 28.4, 28.1; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{42}N_3O_5$, 596.3124; found, 596.3136.

Synthesis of Mesylate 53

To a solution of allyl lactam **52** (155 mg, 0.26 mmol) in THF (9.0 mL) and H_2O (3.0 mL) was added OsO_4 (0.33 mL, 4 wt% solution in water, 0.052 mmol) and NMO (152 mg, 1.30 mmol). The mixture was stirred at rt for 12 h and then a solution of $NaIO_4$ (278 mg) in H_2O (3.0 mL) was added. The mixture was further stirred at rt for 2 h. The cloudy aqueous solution was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting aldehyde was not purified and was used directly in the next step.

To a solution of the crude aldehyde in EtOH (20.0 mL) was added $NaBH_4$ (25 mg, 0.66 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NH_4Cl. After removal of EtOH *in vacuo*, the residue was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The alcohol was not purified and was used directly in the next step.

To a solution of the above crude alcohol in CH_2Cl_2 (10.0 mL) was added TEA (0.18 mL, 1.29 mmol) and MsCl (61 μL, 0.78 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc/TEA, 2/3/0.1 then 3/7/0.1) to give the mesylate **53** (147 mg, 83% for 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.4 Hz, 1H), 7.39-7.28 (m, 5H), 6.97-6.85 (m, 4H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 7.3 Hz, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 4.81, 4.76 (ABq, *J* = 6.7 Hz, 2H), 4.68, 4.61 (ABq, *J* = 11.8 Hz, 2H), 4.51-4.43 (m, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 12.1 Hz, 1H), 3.50 (td, *J* = 4.4, 12.5 Hz, 1H), 3.24-3.18 (m, 1H), 2.95 (s, 3H), 2.72 (s, 3H), 2.53-2.38 (m, 3H), 2.01 (dd, *J* = 3.8, 13.3 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 150.9, 138.9, 137.8, 133.8, 130.8, 128.6, 128.5, 127.8, 127.2, 126.8, 126.2, 124.4, 119.7, 106.4, 94.1, 83.2, 82.0, 69.7, 68.1, 66.6, 59.0, 46.5, 39.4, 36.7, 34.5, 31.4, 28.3, 28.1; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{44}N_3O_8S$, 678.2849; found, 678.2849.

Synthesis of Aldehyde 54

To a solution of mesylate **53** (49 mg, 0.072 mmol) in THF (5.0 mL) was added Pearlman's catalyst (50 mg). After stirring under an atmosphere of hydrogen for 14 h, the reaction mixture was filtered through a pad of Celite and concentrated to give the corresponding alcohol which was not purified but used directly in the next step.

To a solution of the benzyl alcohol in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (35 mg, 0.083 mmol). The reaction was stirred at rt for 15 min and quenched by the addition of 10% aqueous $Na_2S_2O_3$ solution. The aqueous mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/3) to give the aldehyde **54** (30 mg, 75% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.06-6.88 (m, 4H), 6.78 (dd, *J* = 1.0, 7.8 Hz, 1H), 6.50 (dd, *J* = 1.0, 7.9 Hz, 1H), 6.25 (s, 1H), 5.70 (s, 1H), 4.55-4.46 (m, 1H), 4.03-3.92 (m, 1H), 3.41-3.32 (m, 1H), 3.17 (td, *J* = 4.5, 12.8 Hz, 1H), 3.01 (s, 3H), 2.74 (s, 3H), 2.60-2.49 (m, 3H), 1.96 (dd, *J* = 4.4, 13.8 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 172.6, 154.0, 151.1, 138.8, 134.6, 130.8, 130.0, 129.2, 127.6, 127.1, 126.2, 125.0, 117.4, 111.3, 82.6, 82.3, 67.9, 59.7, 46.8, 38.8, 36.7, 34.5, 31.2, 28.0, 27.9; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{28}H_{34}N_3O_7S$, 556.2117; found, 556.2133.

Synthesis of Azide 55

To a solution of the mesylate **54** (25 mg, 0.045 mmol) in DMF (1.5 mL) was added NaN_3 (50 mg, 0.77 mmol). The reaction mixture was stirred at 90 °C for 2 h and diluted with H_2O. The aqueous mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the azide **55** (14 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.11 (dd, *J* = 2.5, 7.6 Hz, 1H), 7.05-6.94 (m, 4H), 6.77 (dd, *J* = 1.1, 7.8 Hz, 1H), 6.49 (dd, *J* = 1.0, 7.9 Hz, 1H), 6.14 (s, 1H), 5.70 (s, 1H), 3.72-3.63 (m, 1H), 3.38-3.32 (m, 1H), 3.17 (td, *J* = 4.7, 12.9 Hz, 1H), 3.00 (s, 3H), 2.92-2.82 (m, 1H), 2.55 (td, *J* = 6.1, 13.3 Hz, 1H), 2.33 (t, *J* = 8.8 Hz, 2H), 1.95 (dd, *J* = 4.5, 13.8 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 172.8, 154.0, 151.1, 138.6, 134.7, 131.2, 130.1, 129.1, 127.5, 126.9, 126.3, 125.1, 117.3, 111.1, 82.7, 82.0, 59.8, 48.7, 47.2, 38.8, 35.1, 31.1, 28.1, 28.0; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{31}N_6O_4$, 503.2407; found, 503.2418.

Synthesis of *α,β*-Unsaturated Ketone 56

To a solution of the aldehyde **55** (130 mg, 0.26 mmol) in acetone (20.0 mL) was added 10% aqueous NaOH solution (2.4 mL). The reaction mixture was stirred at 60 °C for 3 h and then cooled to rt. After removal of acetone *in vacuo*, the cloudy aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1/1) to give the *α,β*-unsaturated ketone **56** (130 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 2.0, 6.6 Hz, 1H), 7.59 (d, *J* = 16.0 Hz, 1H), 6.98-6.91 (m, 4H), 6.35 (t, *J* = 7.9 Hz, 2H), 6.20 (d, *J* = 16.0 Hz, 1H), 5.74 (s, 1H), 5.63 (s, 1H), 3.66-3.59 (m, 1H), 3.29-3.26 (m, 1H), 3.16 (td, *J* = 4.4, 12.7 Hz, 1H), 3.00 (s, 3H), 2.89-2.82 (m, 1H), 2.55-2.44 (m, 1H), 2.49 (s, 3H), 2.31 (t, *J* = 8.6 Hz, 2H), 2.02-1.95 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 173.2, 154.0, 151.1, 145.1, 138.8, 132.7, 131.5, 131.2, 129.1, 128.6, 127.4, 126.9, 125.9, 124.7, 118.6, 107.8, 82.6, 81.9, 58.9, 48.8, 46.5, 39.4, 35.2, 31.1, 28.8, 28.1, 26.5; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{30}H_{35}N_6O_4$, 543.2720; found, 543.2720.

Synthesis of N-Boc Lactam 57

To a solution of lactam **56** (130 mg, 0.24 mmol) in THF (40.0 mL) was added LiHMDS (0.26 mL, 1.0 M in THF, 0.26 mmol) and $(Boc)_2O$ (63 mg, 0.29 mmol). The reaction mixture was stirred at rt for 10 min and quenched with aqueous saturated $NaHCO_3$. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 9/1, 3/1 then 1/1) to give N-Boc-lactam **57** (125 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 16.0 Hz, 1H), 6.97-6.88 (m, 4H), 6.32 (t, *J* = 7.2 Hz, 2H), 6.21 (d, *J* = 16.0 Hz, 1H), 5.61 (s, 1H), 3.63 (dd, *J* = 4.0, 13.3 Hz, 1H), 3.52-3.38 (m, 2H), 2.95 (s, 3H), 2.91-2.81 (m, 1H), 2.51 (td, *J* = 5.6, 13.6 Hz, 1H), 2.37 (s, 3H), 2.37-2.30 (m, 2H), 2.01-1.96 (m, 1H), 1.48 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 171.5, 153.9, 152.8, 150.8, 143.2, 138.5, 133.1, 132.7, 131.1, 129.2, 128.4, 127.5, 127.0, 125.5, 124.9, 118.7, 107.7, 83.9, 82.4, 81.9, 59.0, 48.4, 48.2, 44.0, 34.2, 31.0, 29.4, 28.0, 27.6, 26.4; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{35}H_{43}N_6O_6$, 643.3244; found, 643.3247.

Synthesis of Spiro-*γ*-Lactam 58

To a solution of the N-Boc lactam **57** (140 mg, 0.22 mmol) in THF (60.0 mL) and H_2O (12.0 mL) was added PMe_3 (2.0 mL, 1.0 M in THF, 2.0 mmol). The reaction mixture was stirred at 70 °C for 13 h and then cooled to rt. After removal of THF *in vacuo*, the cloudy aqueous mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/

EtOAc, 1/3) to give the spiro-γ-lactam **58** (118 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (br s, 0.5H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.20 (br s, 0.8H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.98-6.93 (m, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.04 (s, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.66 (s, 0.8H), 3.44-3.38 (m, 1H), 3.21 (t, *J* = 9.7 Hz, 1H), 2.99-2.92 (m, 2H), 2.78 (br s, 2H), 2.37 (s, 3H), 2.42-2.37 (br m, 1H), 2.05-1.98 (m, 1H), 1.52 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 176.0, 155.4, 153.8, 151.6, 143.5, 137.5, 136.9, 134.1, 129.3, 126.7, 125.9, 125.4, 125.3, 114.5, 105.6, 82.3, 81.6, 79.2, 62.1, 52.8, 40.1, 37.7, 35.5, 34.6, 30.0, 28.3, 28.2, 27.4; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{35}H_{45}N_4O_6$, 617.3339; found, 617.3342.

Synthesis of Allylic Alcohol 59

To a solution of the spiro-γ-lactam **58** (113 mg, 0.18 mmol) in THF (30.0 mL) was added MeLi (0.57 mL, 1.6 M in Et_2O, 0.91 mmol) dropwise at −78 °C. The reaction mixture was stirred at -78 °C for 15 min and then quenched with saturated aqueous $NaHCO_3$. After removal of THF *in vacuo*, the residue was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc) to give the allylic alcohol **59** (85 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.27 (br s, 0.8H), 7.21 (br s, 0.6H), 7.12 (td, *J* = 1.2, 7.4 Hz, 1H), 6.99-6.89 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.10 (d, *J* = 11.2 Hz, 1H), 5.90 (s, 0.8H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.80 (br s, 0.8H), 4.27 (br s, 0.8H), 3.46-3.40 (m, 1H), 3.24 (t, *J* = 9.7 Hz, 1H), 3.09 (br s, 1H), 2.99-2.91 (m, 1H), 2.83-2.79 (m, 1H), 2.72-2.64 (br m, 1H), 2.47 (s, 3H), 2.18-2.06 (m, 1H), 1.92-1.84 (m, 1H), 1.51 (s, 9H), 1.41 (s, 3H), 1.37 (s, 9H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 155.7, 153.9, 150.8, 138.9, 138.3, 137.6, 137.1, 129.0, 126.4, 126.1, 125.2, 124.9, 123.4, 114.7, 103.7, 82.8, 81.3, 79.6, 70.5, 60.4, 52.8, 40.1, 38.1, 35.4, 35.1, 30.7, 30.0, 28.8, 28.4, 28.3; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{49}N_4O_6$, 633.3652; found, 633.3647.

Synthesis of Hexacyclic γ-Lactam 61 and Diene 60

To a solution of the allylic alcohol **59** (83 mg, 0.13 mmol) in $CHCl_3$ (20.0 mL) was added PPTS (3.3 mg, 0.013 mmol). The reaction mixture was stirred at rt for 1.5 h. After removal of $CHCl_3$ *in vacuo*, the residue was purified by flash column chromatography on silica gel (hexanes/acetone, 5/1) to give the hexacycle **61** (51 mg, 62%) and diene **60** (20 mg, 24%).

Hexacycle 61—^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (br m, 1H), 7.26-7.23 (br m, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.92 (td, *J* = 1.3, 7.7 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 6.28 (br d, *J* = 6.7 Hz, 1H), 5.98 (br s, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 5.84 (s, 1H), 5.55 (br s, 1H), 5.10 (br s, 1H), 3.91 (br s, 1H), 3.47 (br d, *J* = 9.0 Hz, 1H), 3.14-2.90 (m, 4H), 2.45 (s, 3H), 2.14-2.09 (br m, 1H), 1.98-1.92 (br m, 1H), 1.84 (s, 3H), 1.75 (s, 3H), 1.51 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 156.2, 153.5, 150.6, 139.3, 137.3, 133.3, 128.8, 126.4, 125.9, 125.1, 125.0, 124.3, 116.9, 103.2, 89.5, 81.2, 79.6, 61.2, 59.7, 52.3, 41.0, 39.2, 36.1, 30.7, 28.6, 28.4, 25.6, 18.9; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{47}N_4O_5$, 615.3546; found, 615.3560.

Diene 60—^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.45 (br s, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.97 (td, *J* = 1.4, 7.8 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 14.6 Hz, 1H), 6.74 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 5.97 (s, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 4.42 (br s, 1H), 3.48-3.42 (m, 1H), 3.26 (t, *J* = 9.8 Hz, 1H), 3.01-2.94 (m, 2H), 2.82 (br s, 1H), 2.52 (s, 3H), 2.46-2.37 (m, 1H), 2.03-1.86 (m, 1H), 1.91 (s, 3H), 1.53 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 155.4, 151.3, 142.3, 138.2, 137.2, 131.5, 129.1, 128.2, 126.6, 126.1, 125.3, 125.1, 123.5, 116.7, 114.4, 103.9, 82.9, 81.4, 79.2, 61.5, 52.7, 40.1, 37.8, 35.2, 30.6, 28.4, 28.3, 19.2; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{36}H_{47}N_4O_5$, 615.3546; found, 615.3554.

Synthesis of Methyl Imidate 62

To a solution of the hexacycle **61** (12.0 mg, 0.020 mmol) in CH_2Cl_2 (10.0 mL) was added DIPEA (34 μL, 0.20 mmol) and Me_3OBF_4 (29 mg, 0.20 mmol). The reaction mixture was stirred at rt for 30 min and quenched with saturated aqueous $NaHCO_3$. The solution was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (hexanes/acetone, 2/1) to give the methyl imidate **62** (10.5 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.4 Hz, 1H), 7.13 (td, *J* = 1.4, 7.5 Hz, 1H), 6.95-6.89 (m, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.33 (br s, 1H), 5.96 (d, *J* = 6.8 Hz, 1H), 5.68 (s, 1H), 5.18 (br s, 1H), 3.92-3.65 (m, 4H), 3.78 (s, 3H), 3.48-3.36 (br m, 1H), 3.26-3.14 (br m, 1H), 2.98-2.73 (br m, 2H), 2.38 (s, 3H), 2.24-2.15 (m, 1H), 1.84 (s, 3H), 1.74 (s, 3H), 1.51 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.8, 153.5, 150.7, 140.3, 136.8, 128.4, 126.3, 125.0, 124.9, 124.8, 124.5, 116.9, 103.5, 81.4, 80.2, 59.1, 57.9, 55.6, 51.1, 40.1, 38.4, 31.2, 29.7, 28.5, 28.4, 25.7, 18.8; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{37}H_{49}N_4O_5$, 629.3703; found, 629.3723.

Synthesis of Amidine 63

To a solution of the imidate **62** (13.0 mg, 0.021 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (0.25 mL). The reaction mixture was stirred at rt for 45 min and quenched with saturated aqueous $NaHCO_3$. The solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (hexanes/acetone, 2/1) to give the amidine 63 (9.0 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07-6.96 (m, 2H), 7.05 (dd, *J* = 1.4, 7.4 Hz, 1H), 6.86 (t, *J* = 8.5 Hz, 1H), 6.78 (t, *J* = 7.7 Hz, 1H), 6.05 (dd, *J* = 7.9, 12.9 Hz, 2H), 5.79 (br s, 0.6H), 5.61 (br s, 0.4H), 5.36-5.31 (m, 1H), 4.81 (d, *J* = 8.7 Hz, 1H), 3.83-3.73 (m, 2H), 3.36-3.29 (m, 1H), 3.26-3.18 (m, 1H), 2.90 (s, 3H), 2.87-2.77 (m, 1H), 2.29-2.20 (m, 1H), 2.07-2.00 (m, 1H), 1.85 (br s, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.42 (br s, 5H), 1.23 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 154.0, 149.6, 137.7, 136.6, 134.3, 130.2, 129.7, 128.5, 127.5, 126.6, 124.6, 123.9, 121.9, 116.9, 104.3, 81.0, 79.1, 60.1, 58.6, 54.9, 54.8, 45.5, 38.3, 30.4, 28.3, 27.0, 25.7, 18.6; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{31}H_{37}N_4O_2$, 497.2917; found, 497.2918.

Synthesis of (±)-Communesin F (8)

To a solution of the amidine **63** (14.0 mg, 0.028 mmol) in acetic acid (0.8 mL) and acetic anhydride (0.8 mL) was added $NaBH_4$ (90 mg, 2.38 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and quenched with saturated aqueous Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting N-acetyl-N-Boc-bis-aminal **64** was not purified and was used directly in the next step.

To a solution of the bis-aminal **64** in CH_2Cl_2 (5.0 mL) was added TFA (2.0 mL). The reaction mixture was stirred at rt for 12 h and quenched with saturated aqueous Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/acetone, 5/1 then 2/1) to give (±)-communesin F (**8**) (8.2 mg, 66% for 2 steps).

As described by the Qin group[6], (±)-communesin F exists as two amide rotamers in a ratio of 2.6: 1 in $CDCl_3$ as shown by ^{1}H NMR. Only the NMR data for the major rotamer is listed (see Supporting Information for copies of the spectra):

Major rotamer of 8—^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 1.7, 7.7 Hz, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 6.72-6.64 (m, 3H), 6.06 (d, *J* = 7.7 Hz, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 5.21 (br d, *J* = 8.9 Hz, 1H), 5.09 (s, 1H), 5.03 (d, *J* = 8.8 Hz, 1H), 4.64 (s, 1H), 3.83 (dd, *J* = 8.8, 11.4 Hz, 1H), 3.76 (br s, 0.5H), 3.34-3.27 (m, 1H), 3.25-3.17 (m, 1H), 3.04-2.96 (m, 1H), 2.80 (s,

3H), 2.75-2.70 (m, 1H), 2.38 (s, 3H), 2.30-2.18 (m, 2H), 1.97-1.91 (m, 1H), 1.83 (d, J = 1.2 Hz, 3H), 1.76 (d, J = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 150.1, 142.7, 140.6, 136.1, 132.7, 131.3, 128.3, 127.3, 124.6, 123.2, 120.6, 117.0, 114.7, 100.7, 82.6, 79.5, 64.4, 51.8, 51.2, 44.2, 37.8, 36.2, 30.8, 29.6, 26.0, 22.6, 18.5; HRMS-ES (*m/z*): $[M + H]^+$ calcd for $C_{28}H_{33}N_4O$, 441.2654; found, 441.2635.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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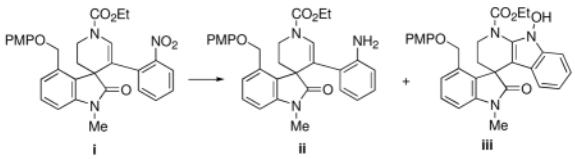

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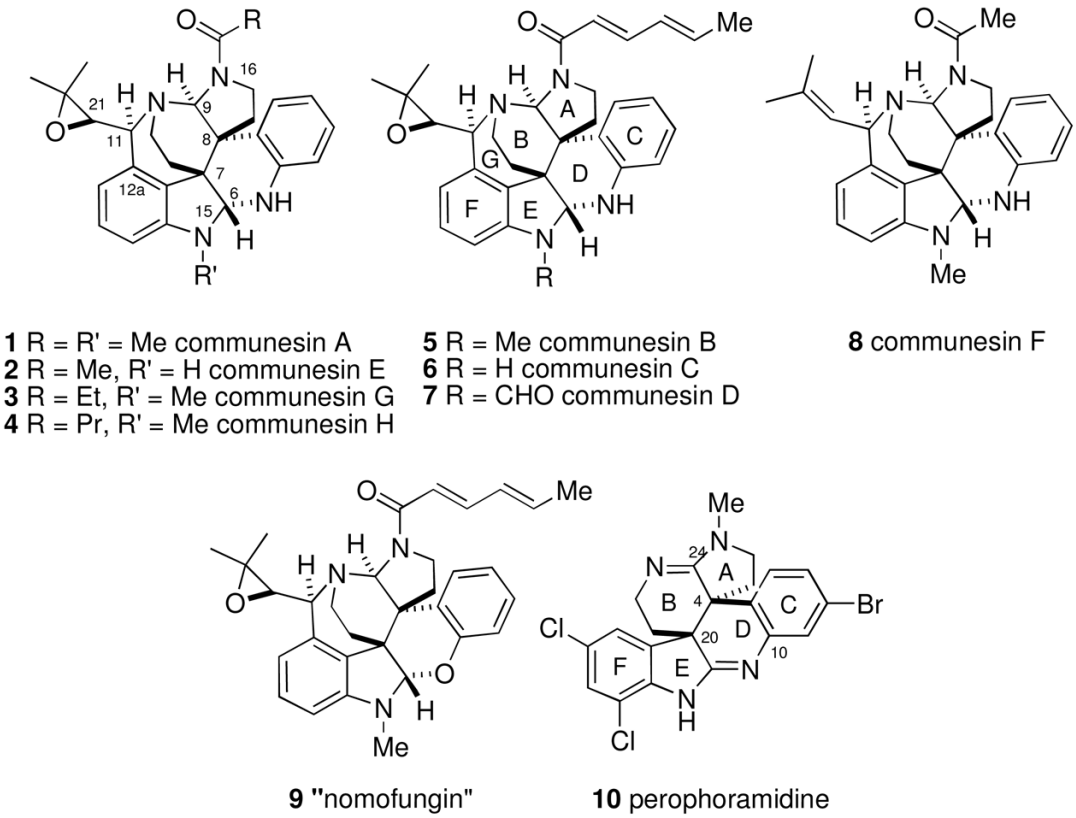
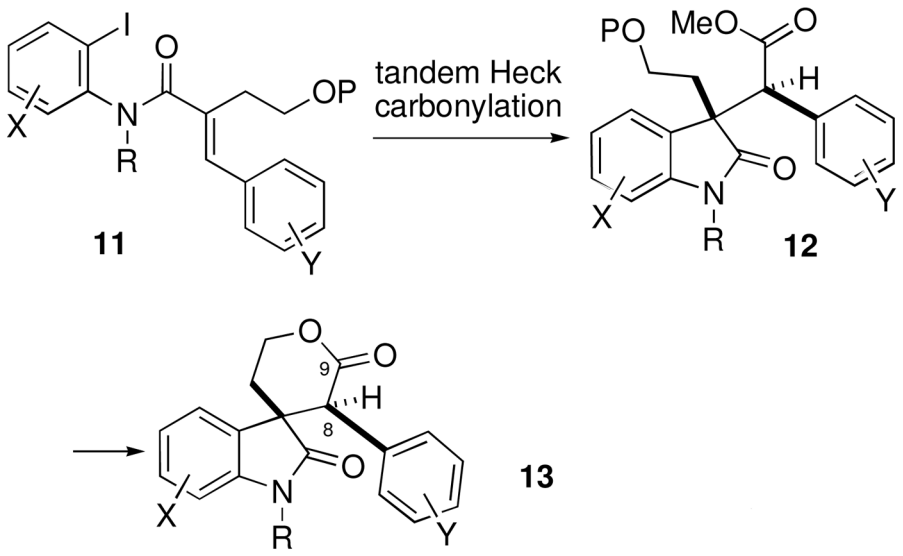


FIGURE 1.
The Communesins and Perophoramidine



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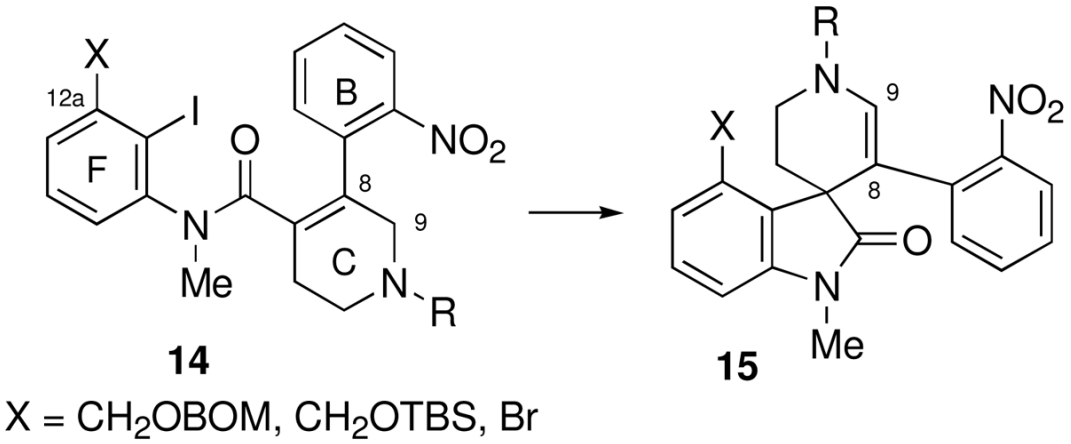

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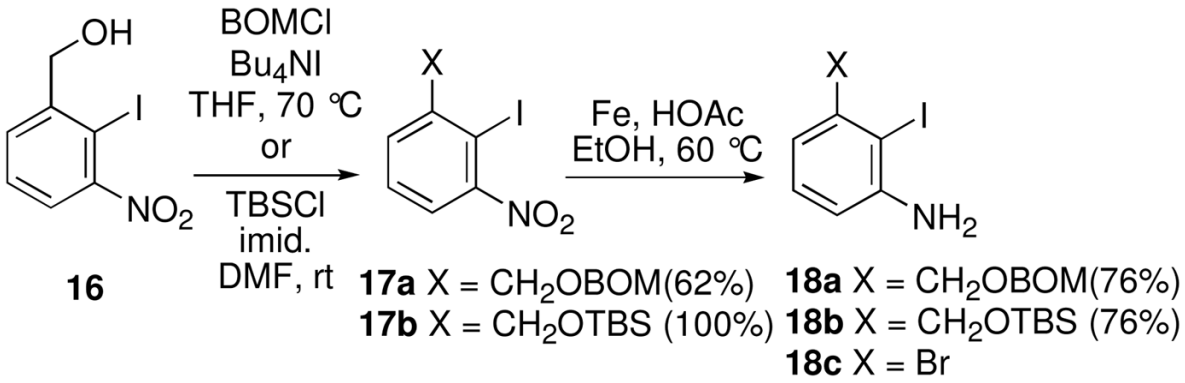

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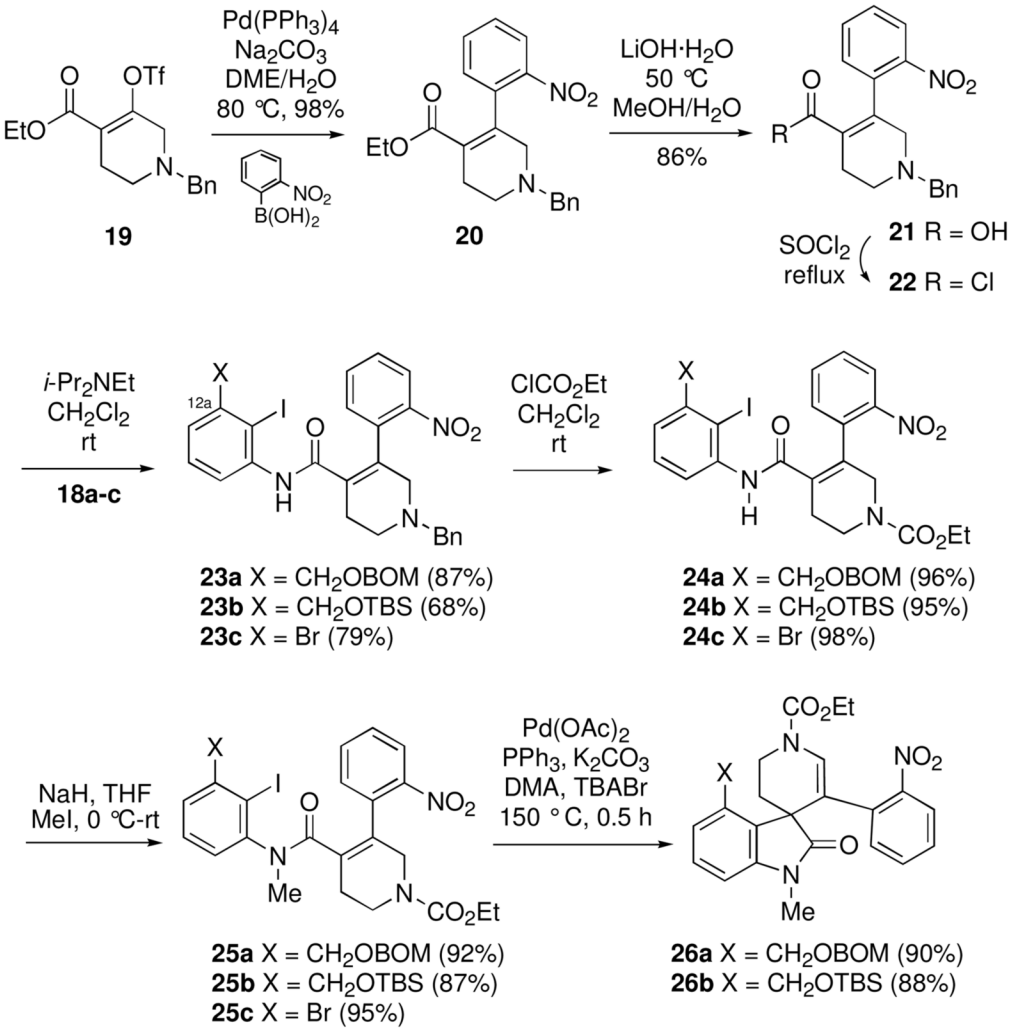

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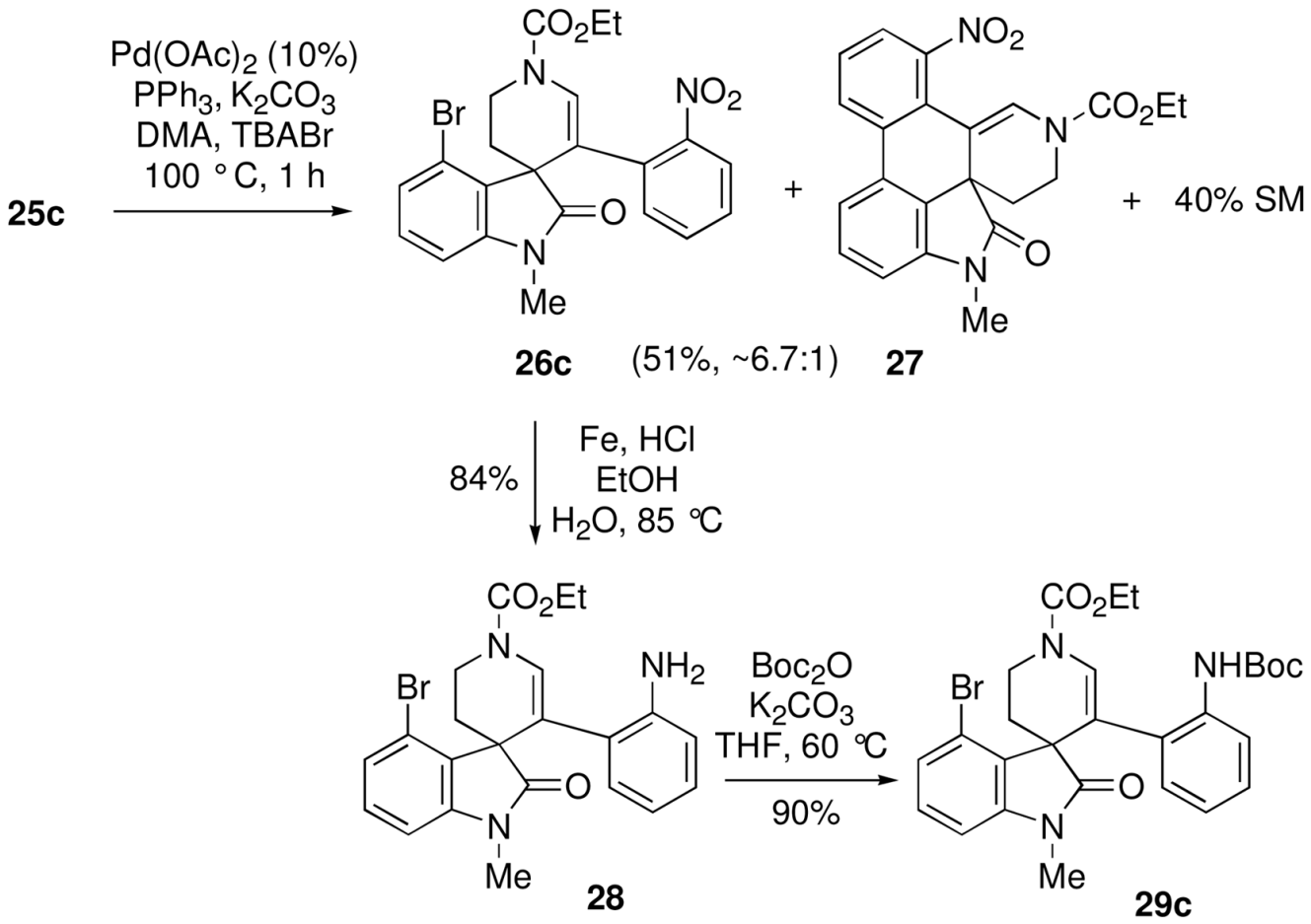

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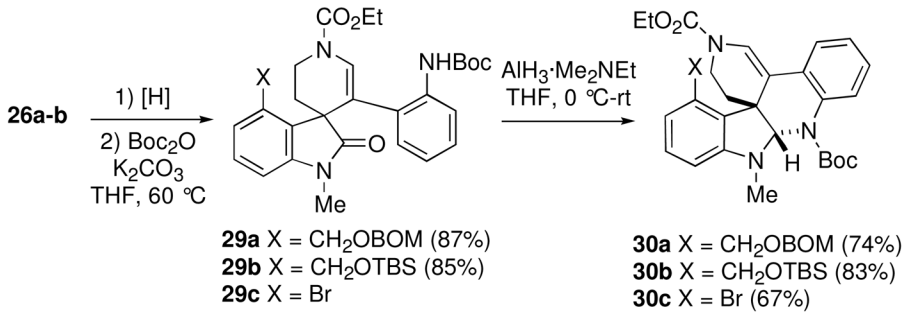

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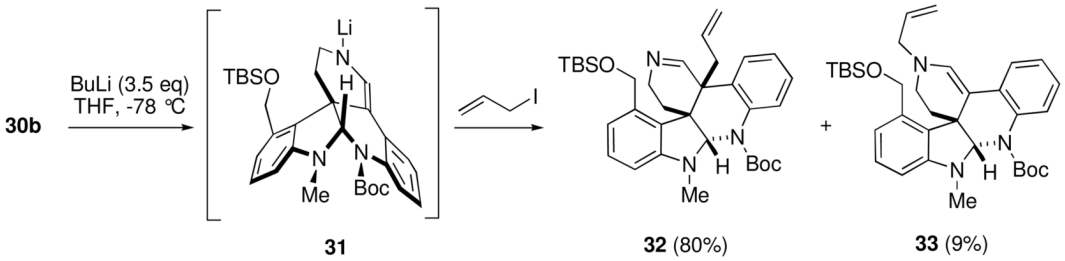

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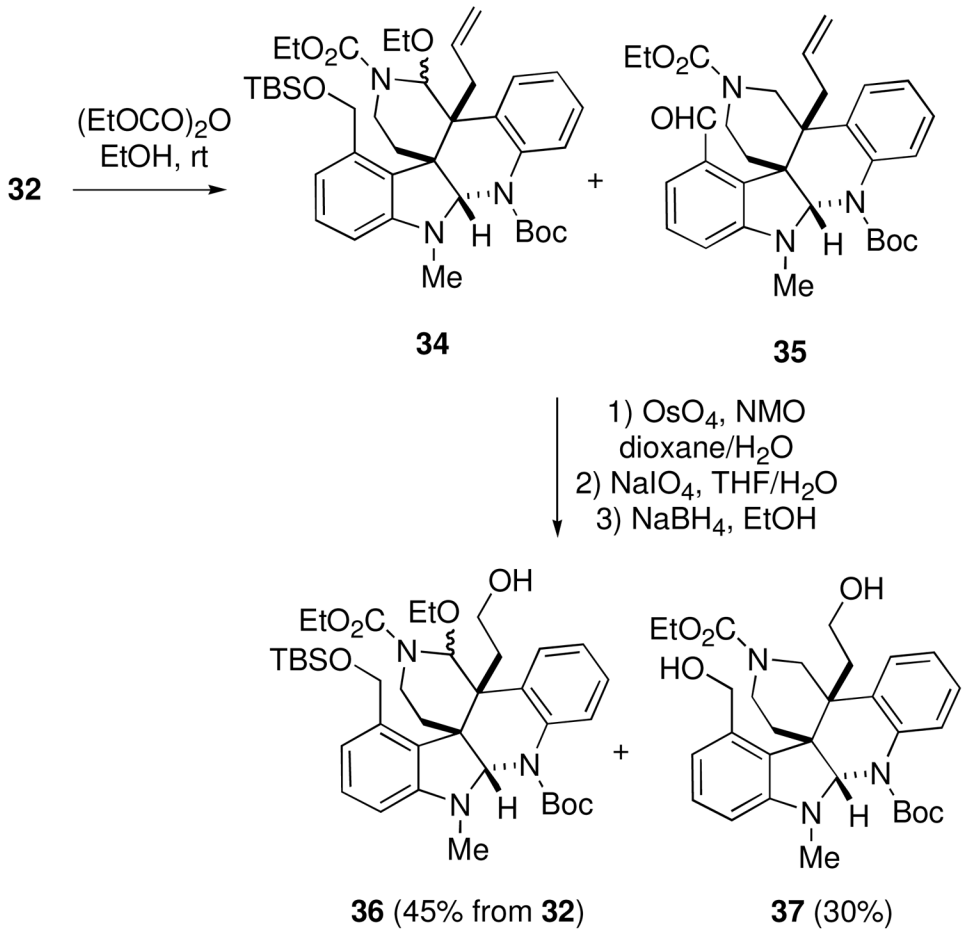

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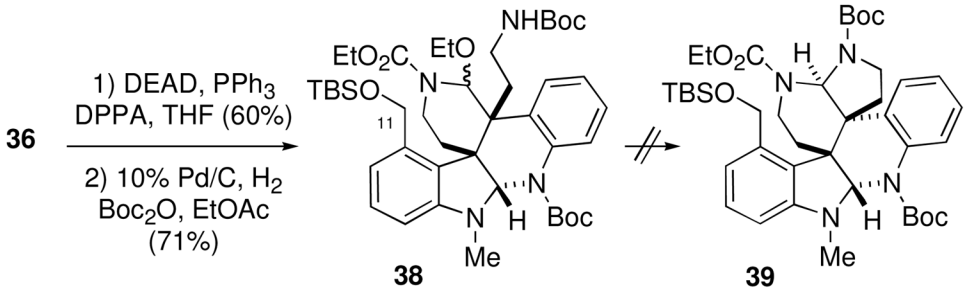

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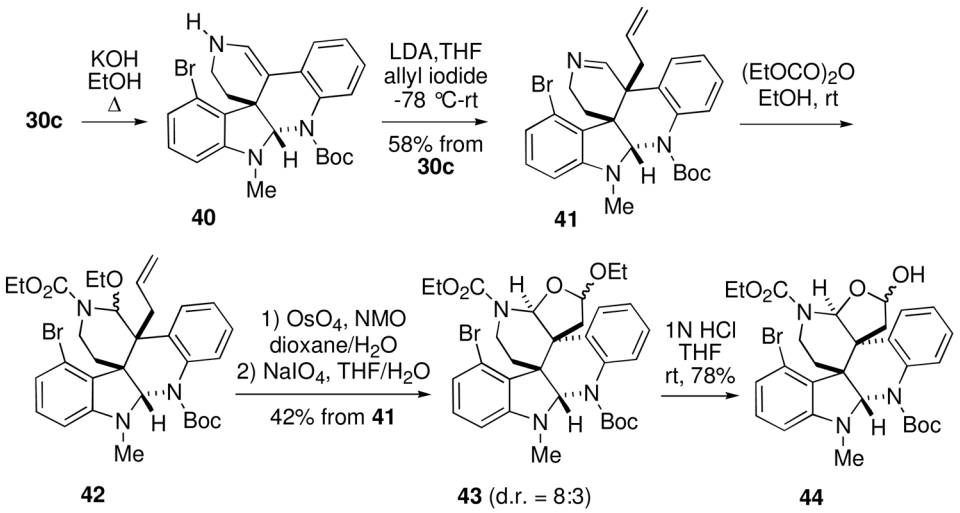

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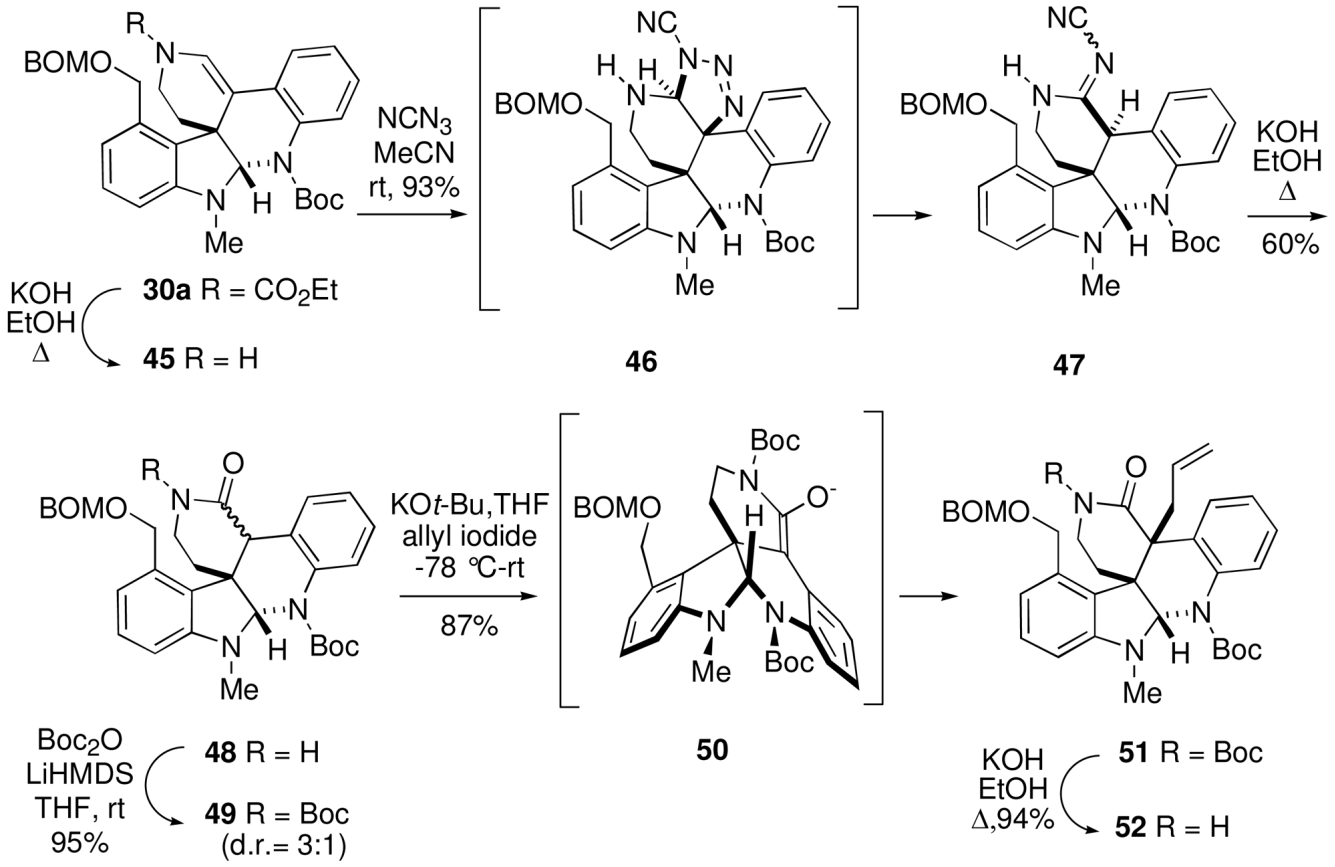

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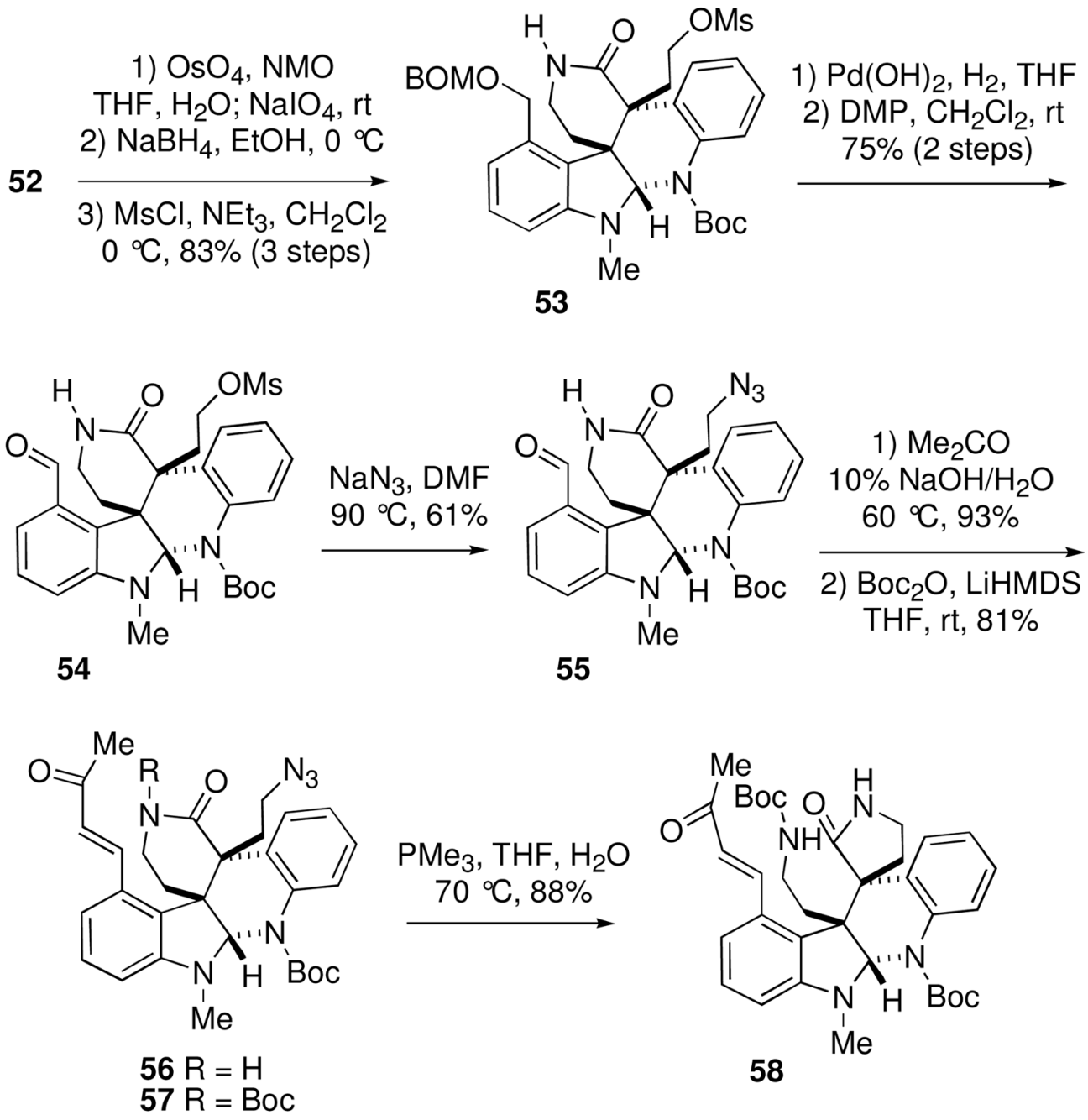

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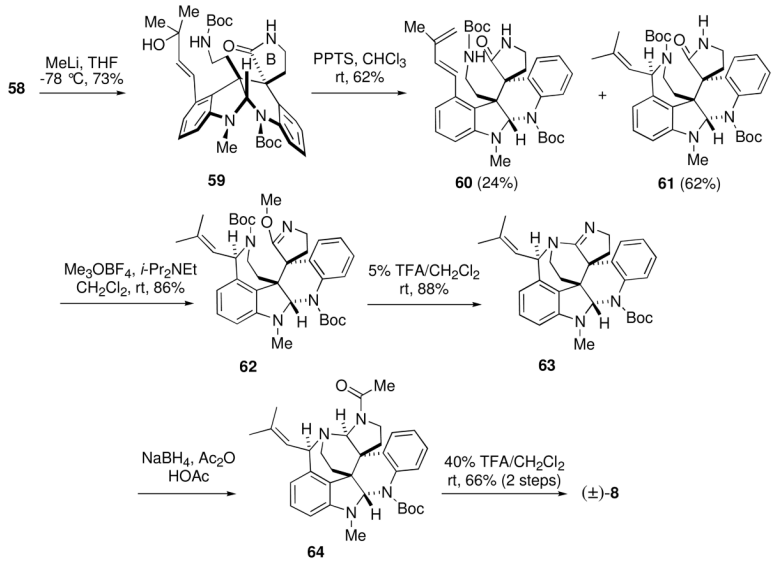

SCHEME 13.