

ペロフロラミジンの全合成研究

2013

京都大学大学院 薬学研究科
創薬科学専攻 薬品分子化学分野

石田 貴之

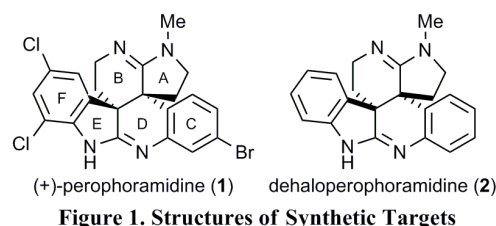
目次

第一章 研究背景と本研究の概要	
第一節 ペロフォラミジンに関する諸知見	2
第二節 ペロフォラミジンおよび関連する天然物の全合成ならびに合成研究	4
第三節 本研究の概要と構成	8
第二章 ヨウ化サマリウム(II)による還元的環化反応を鍵反応とする骨格構築	
第一節 ヨウ化サマリウム(II)を用いた還元的環化反応の開発	10
第二節 還元的環化反応による五環性アミジンの合成	19
第三章 脱芳香族共役付加反応を鍵反応とする骨格構築	
第一節 脱芳香族共役付加反応の開発とデハロペロフォラミジンの合成	24
第二節 脱芳香族共役付加反応によるハロゲン化六環性ビスアミジンの合成	32
結論	38
参考文献	39
実験項	44
発表論文目録	87
謝辞	88

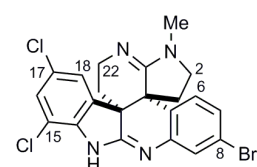
第一章 研究の背景

第一節 ペロフォラミジンに関する諸知見

Perophoramidine (**1**, **Figure 1**)は2002年にIrelandらによって単離、構造決定、生物活性が報告された海産性のアルカロイドである¹。Irelandらはフィリピン内ゼンボアング近海で採取されたホヤの一種である *Perophora*



namei Hartmeyer and Michaelsonのメタノール抽出液を精製することで**1**を単離した。高分解能FAB-MSスペクトルより推定される**1**の構造は二つの塩素原子と単一の臭素原子を有するものであり、これは**1**を接触還元によって脱ハロゲン化することで得られた**2**の分析によって示された。なお、誘導体**2**はIrelandらによる合成に際してdehalogenated perophoramidineと命名されたが、後の合成研究でRainierらがdehaloperophoramidineと称した²ことにより後者の名称が一般化している。天然物**1**の高度に縮環した構造は、2D INADEQUATEを含む各種NMRスペクトルの解析によって二連続の第四級炭素 (all-carbon quaternary carbon center)を含む六環性ビスアミジンであると推定され、中心部の相対立体配置はROESYスペクトルにおける相関関係 (H6-H2b, H18-H3b, H18-H22a, **Figure 2**)およびモデルによるエネルギー評価から*trans*体と決定された。二種のハロゲン原子の結合位置に関しては、計算化学による¹³C NMRシフト値予測が利用され、C8-ブロモ-C15,C17-ジクロロ体が実測値とよい一致を示したことから決定がなされた。また、同報告において**1**はヒト結腸癌細胞HCT116に対して60 μMの50%阻害濃度 (IC₅₀)を示し、24時間以内にポリADPリボースポリメラーゼ (PARP)の分解によるアポトーシス誘導を起こすことが明らかとされた。



1と類似の構造を有する天然物として、八種の類縁体からなる communesin 類 (**3-10**, **Figure 3**)が知られている。初期にはcommindolin B,Aとして英国のPfizer研究所で見出さ

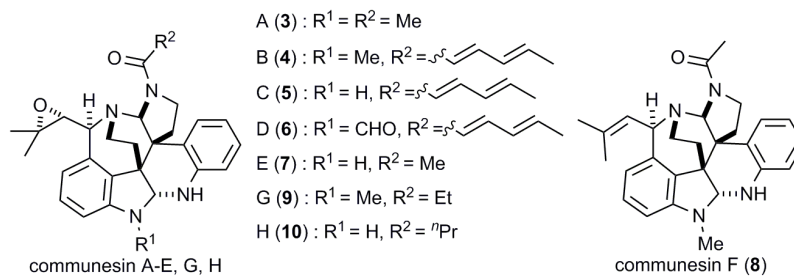
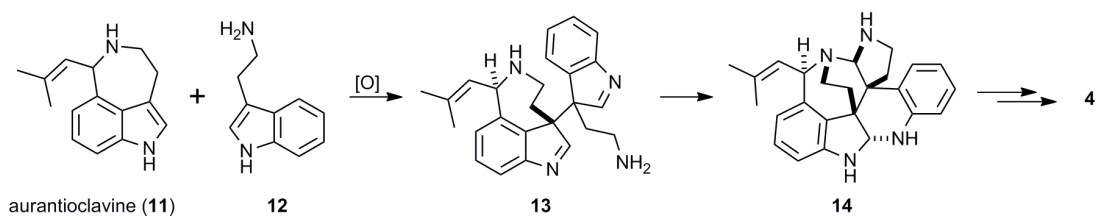


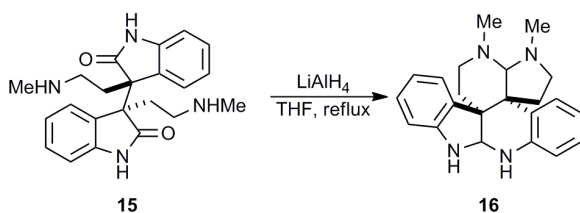
Figure 3. Structures of Related Natural Products, Communesins

れた³との説がある communesin A,B (**3,4**)は、1993年にNumataらによる単離が報告された⁴。Numataらは海藻の一種である *Enteromorpha intestinalis* に付着した *Penicillium* 属の菌類より communesin A,B を単離し、NOE測定によってその構造が高度縮環型七環性ビスアミナールを含むものであることを明らかにした。後にこれら天然物の類縁体である communesin C-Hの単離が報告されたが⁵、それ

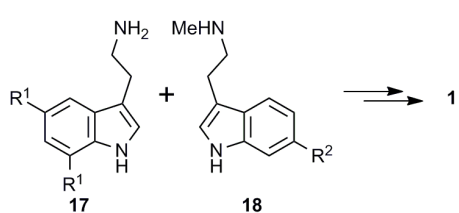
らに共通する骨格はいずれも、その二連続第四級炭素の相対立体配置が異なる点およびビスアミンがビスアミナールに代替されている点で差異を有するものの、**1**と同様の含窒素六環性骨格である。Stoltzらは、関連する天然物nomofunginがcommunesin Bと同一の化合物であると主張する文献においてcommunesin類の生合成経路について考察を加えており⁶、真菌性アルカロイドであるaurantioclavine (**11**)とtryptamine (**12**)の酸化的二量化による中間体**13**を経て生じる多環性コア**14**に対して適切な官能基化がなされることで**4**が生成する可能性を示唆している (Scheme 1)。インドールの酸化的二量化によって合成したmeso体**15**に対してLiAlH₄を作用させることでHendricksonらが六環性ビスアミナール**16**を得ている実験的背景 (Scheme 2)⁷を踏まえ、Stoltzらは同文献内で**1**の生合成経路もcommunesin類と同様のtryptamine誘導体 (**17,18**)の酸化的二量化反応によって説明できると論じている (Scheme 3)。



Scheme 1. Proposed Biosynthetic Pathway of Communesin



Scheme 2. Supportive Experiment by Hendrickson

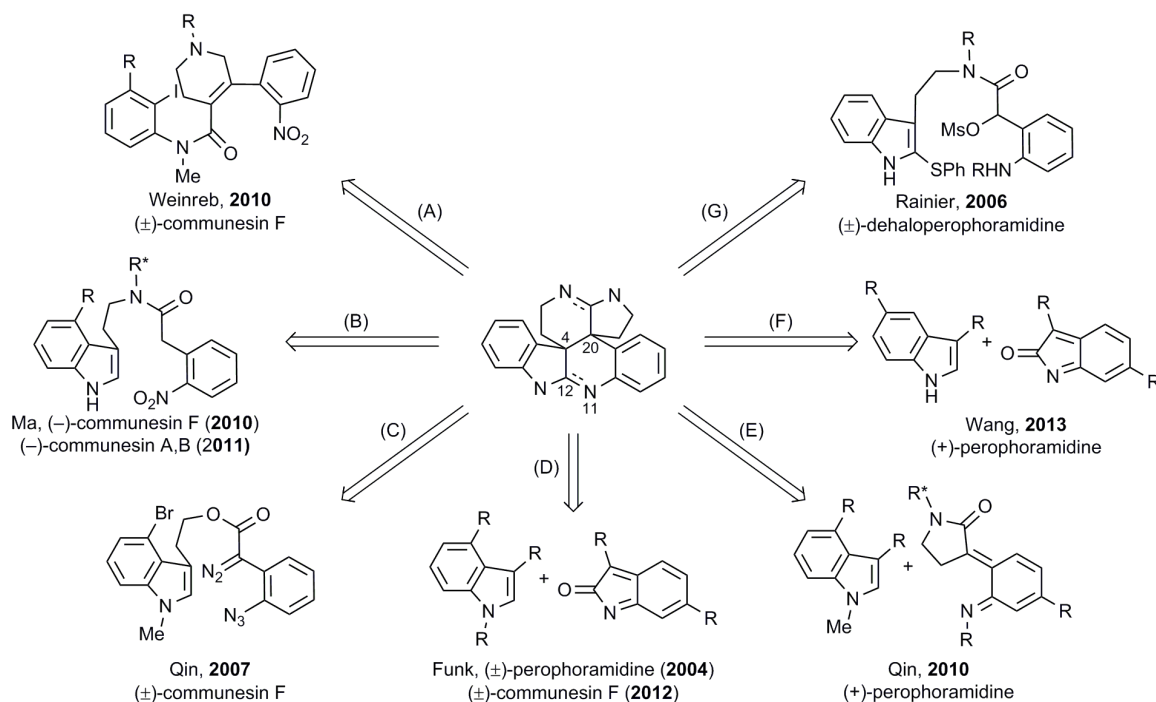


Scheme 3. Biosynthesis of Perphoramidine

第二節 ペロフォラミジンおよび関連する天然物の全合成ならびに合成研究

第一節で述べた perophoramidine (**1**)および構造的に類似した communesin 類(**3-10**)は、その生物活性のみならず、他に類を見ない複雑な多環性構造により有機合成化学者の興味を集め、結果として多くの合成研究がなされることとなった。2013 年末時点で、**1** の全合成に関してはラセミ合成が 1 件⁸および不斉合成が 2 件^{9,10}報告されており、Ireland によって **1** より誘導された dehaloperophoramidine (**2**)についてはラセミでの合成が 1 件²報告されている。また、communesin 類については communesin F (**8**)のラセミ合成が 3 件^{11,12,13}および不斉合成が 1 件¹⁴、communesin A,B (**3,4**)の不斉合成が 1 件¹⁵それぞれ報告されている。詳細については割愛するが、その他これまでに数多くの合成研究^{16,17}が報告されている。本節では、既存の骨格構築法が概ね同一の合成戦略に基づいていることを俯瞰し、**1** の合成において多環性アミジンの直接的かつ効率的構築法が未開拓の課題であったことを示す。

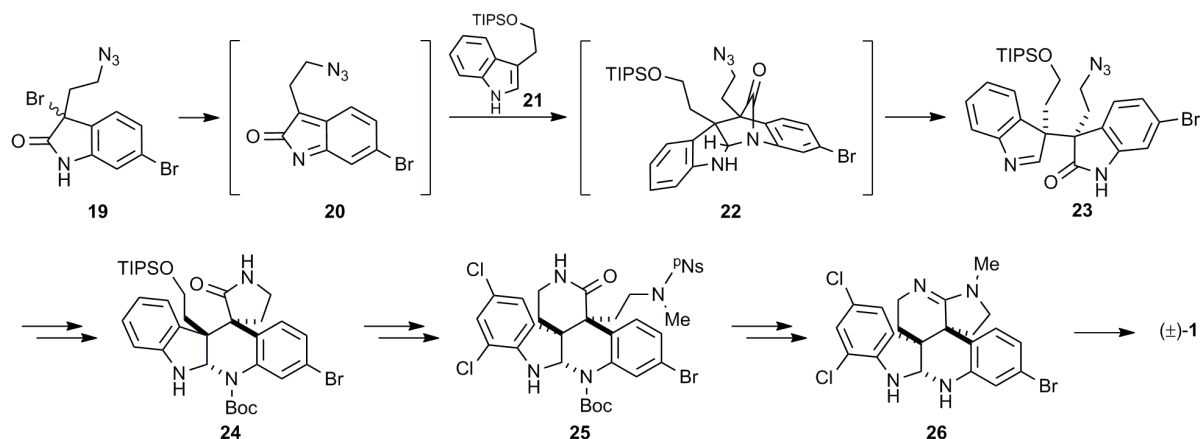
これまでに報告された **1,2** および communesin 類の合成で利用されている多環性アミジンあるいはアミナルの構築法は以下の通りである (Scheme 4)。Weinreb による分子内 Heck 反応を用いたスピロオキシインドール合成法¹² (A)を唯一の例外として、既存の多環性骨格構築法は全て Stoltz らによって提唱された生合成経路と同様の、tryptamine 類縁体を原料とした C4-C20 および N11-C12 の結合形成に基づいていることが明らかである (骨格中の番号は perophoramidine に準拠)。特に、**1** の全合成 (D⁸, E⁹, F¹⁰)についてはインドールとキノンメチドイミンとの反応を利用している点で完



Scheme 4. Reported Synthetic Strategies for Construction of Hexacyclic Core

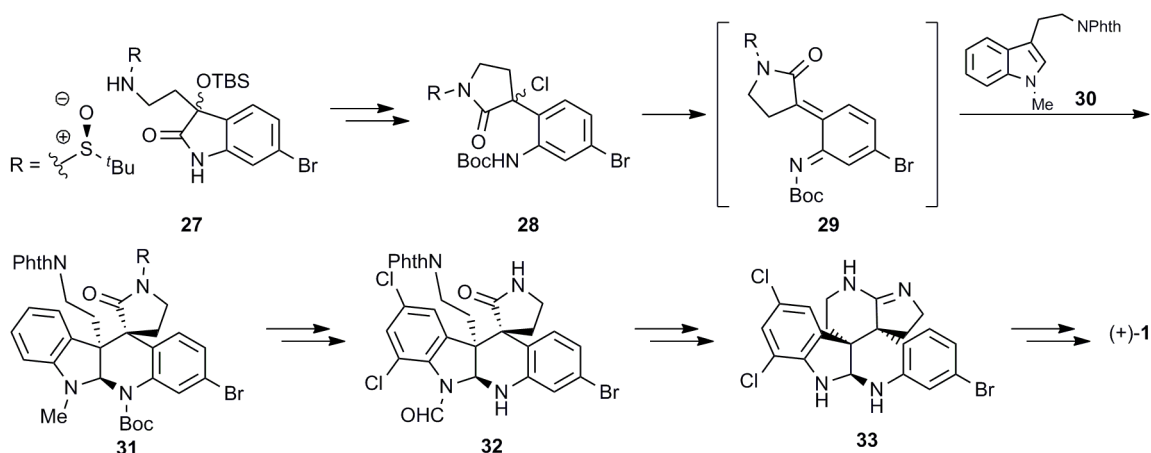
全に同一の合成戦略に則っている。以下、これまでに達成された **1** の全合成 (D,E,F) および **2** の合成 (G) について紹介する。

Funk らが 2004 年に報告した **1** のラセミ全合成⁸は、3-ブロモオキシインドール **19** に塩基を作用させて系内で生成させたキノンメチドイミン **20** とインドール誘導体 **21** とのヘテロ Diels-Alder 反応を鍵反応としている (Scheme 5)。付加体であるアминаール中間体 **22** を経て >20:1 の選択性で得られた生成物 **23** のオキシインドール窒素上に電子求引性保護基を付与し、ラクタム環の組み換えを行ってスピロラクタム **24** とした。この化合物 **24** を塩素化した後、ラクタム環の組み換えを含む各種の変換反応を経て六員環ラクタム **25** を合成し、六環性アминаール **26** の構築後に二酸化マンガンによってアминаール **26** をアミジンへ酸化することで **1** の全合成を達成している。この全合成により、Ireland によって提唱された **1** の構造¹ が妥当であることが合成化学的に証明された。



Scheme 5. Seminal Total Synthesis of (±)-Perophoramidine by Funk

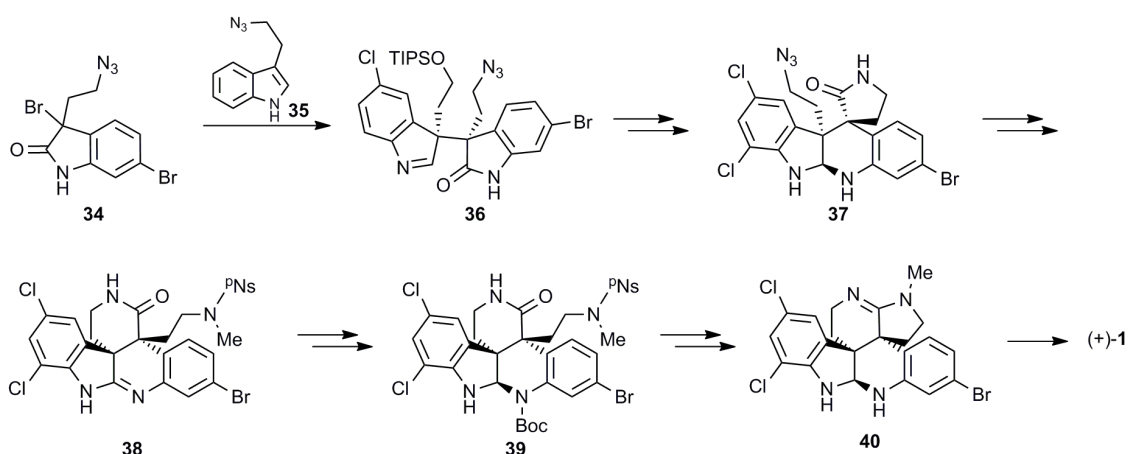
2010 年に Qin らによって報告された (+)-**1** の不斉全合成では、キラルスルホキシドが不斉補助基として利用されている⁹ (Scheme 6)。合成戦略は Funk らが利用したものと同一ヘテロ Diels-Alder 反応であるが、Qin らは 3-ヒドロキシオキシインドール誘導体 **27** から Diels-Alder 反応に先んじて五員環ラクタムの構築を行った **28** を鍵反応の原料として用いている。ラクタム **28** から系内調製



Scheme 6. Asymmetric Total Synthesis of (+)-Perophoramidine by Qin

したキノンメチドイミン **29** と、フタルイミドでアミンを保護したトリプタミン誘導体 **30** との Diels-Alder 反応は、銀塩のスクリーニングや溶媒検討の結果、11:1 のジアステレオ選択性で目的物を与える結果となった。これによって得られた **31** に対して塩素化と不斉補助基の除去などを行って化合物 **32** とし、イミデートへの変換やアミジンの環化などを経て六環性アミナル **33** とした後、アミナルの酸化に続くアミジンの位置選択的 *N*-メチル化によって (+)-**1** を合成している。不斉全合成が達成されたことにより、天然型である (+)-**1** の絶対立体配置が 4*R*, 20*S* 体 (**Figure 1**) であることが明らかとなった。

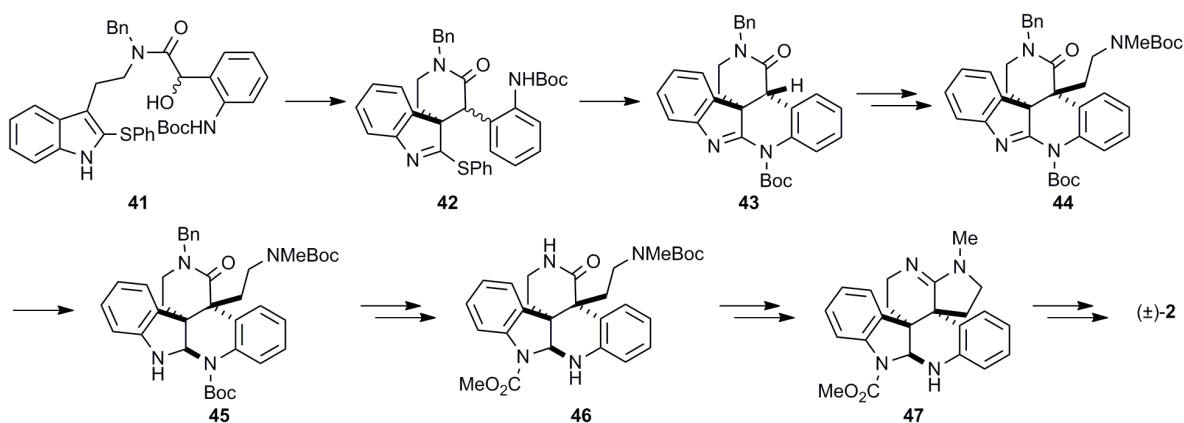
近年報告された Wang らによる触媒的不斉全合成¹⁰も同様の戦略に基づく合成であり、触媒量の酢酸ニッケル(II)と不斉ジアミン配位子存在下、3-ブロモオキシインドール **34** からキノンメチドイミンを生成させることでインドール **35** に対して不斉アルキル化を行い、12:1 のジアステレオ選択性でインドレニン **36** を 90% の鏡像体過剰率で合成した (**Scheme 7**)。この化合物 **36** は数工程を経てスピロラクタム **37** へ誘導されたが、ラクタム環の組み換えとアミナルの酸化などによって五環性アミジン **38** へ変換した後、アミジンの Boc 化と再還元によって Funk の報告した中間体であるアミナル **39** へと導いている。この後、Funk とほぼ同様の手法を用いて六環性アミナル **40** を構築し、アミナルのアミジンへの酸化を経て (+)-**1** を合成した。この合成経路における多環性アミナルからのアミジンへの酸化とアミナルへの還元、そしてアミジンへの再酸化過程は、近年注目される redox economy¹⁸の観点から非効率であると同時に、多環性アミジンの効率的構築法の開発とアミナルの酸化を経由しない六環性骨格への合成経路確立が合成化学上の課題であることを示唆する結果であると言える。



Scheme 7. Catalytic Asymmetric Total Synthesis of (+)-Perophoramidine by Wang

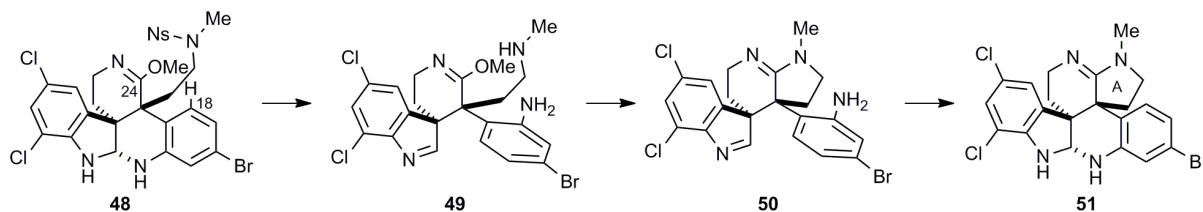
類似の示唆に富む知見は、Rainier らによって 2006 年に報告された **2** のラセミ合成²にも見出すことができる (**Scheme 8**)。Rainier らは、*N*-Boc イサチンから合成した **41** の水酸基を塩基存在下脱

離基へと変換することで、インドール環への求電子的アルキル化が進行してスピロラクタム **42** へと変換され、これを DBU で処理することによって α 位の異性化を伴いながら五環性アミジン **43** が合成できることを見出した。その後、ラクタム α 位の官能基化によって化合物 **44** まで誘導することに成功しているが、以降の検討の結果、化合物 **44** からの直接的な六環性骨格構築を断念している。代替経路として **44** のアミジンを一旦還元後、保護基の付け替えによって合成したアミナール **46** から A 環を構築して六環性アミナール **47** とし、その後アミナールを酸化することで **2** の合成を達成している。



Scheme 8. Synthesis of (±)-Dehaloperophoramidine by Rainier

A 環構築時におけるアミジンとアミナールの差異について、同文献²内で Rainier らは以下のように述べている (Scheme 9)。すなわち、Funk らの報告⁸で円滑に環化が進行した要因は、五環性化合物 **48** のアミナールの開環に伴って 24 位の炭素周りの立体的な混雑が一時的に解消され (**49**)、上部アミジンの閉環後 (**50**) に下部アミナールが再生する (**51**) ことに由来するというものである。また、Rainier らは分子模型での検討から、アミジンからの環化を妨げる立体障害の原因を主として 18 位の水素原子に帰した。



Scheme 9. Proposed Mechanism of A Ring Construction

第三節 本研究の概要と構成

第二節で述べた研究背景を踏まえ、筆者は perophoramidine (**1**)の全合成に向けて多環性アミジンの効率的合成法の開発と、下部アミナル中間体の酸化を経由しない六環性ビスアミジン骨格の直接的構築法を確立すべく研究に着手することとした。筆者は本研究において、いずれも下部アミジンを含む五環性化合物 (**Figure 4**)を共通の鍵中間体とする二つの

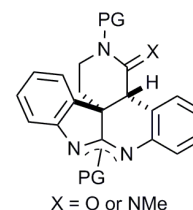
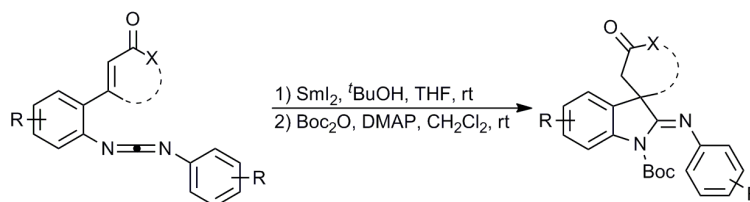


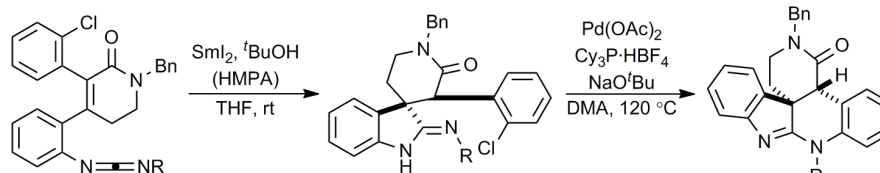
Figure 4. Key Intermediate

合成戦略に基づいて **1** の合成研究に取り組んだ。その結果として、新規な二種のイミノインドリン合成法を見出して鍵中間体の合成を達成し、続く変換によって dehaloperophoramidine (**2**)を含む **1** の六環性ビスアミジン骨格構築を達成した。

本章に続く第二章では、ヨウ化サマリウム(II)(SmI₂)によるイミノインドリン合成法の開発と **1** の五環性骨格構築への応用について述べる。筆者は、分子内に不飽和カルボニル部位を有するカルボジイミドに対して *tert*-ブチルアルコール存在下 SmI₂ を作用させ、続いて Boc 基による保護を行うことで、温和な条件下良好な収率で 2-イミノインドリンが合成できることを見出し、基質一般性の検討によって本反応は各種の置換基を許容する官能基共存性に優れた反応であることを明らかにした (**Scheme 10**)。更に、ラクタム α 位にアリール基を有する基質に対して本反応を適用することで四環性スピロイミノインドリンを合成し、続くパラジウム触媒による塩化アリールとアミジン窒素との環化反応によって **1** の五環性骨格を有するアミジンへ誘導した (**Scheme 11**)。



Scheme 10. SmI₂-Mediated Reductive Cyclization of Carbodiimides



Scheme 11. Application of Reductive Cyclization to Construction of Pentacyclic Core

還元的環化反応を利用した第一世代の合成戦略では下部アミジン上の保護基の選択に制限があったことを主要因として、筆者は同一の五環性アミジン中間体を合成標的とした新たな合成戦略を設定することとした。第二世代の合成戦略は、2-ヨードフェニル基を分子内に有する 2-アミノキノリン (**Figure 5**)からリチウム-ヨウ素交換反応によって生成したアリールリチウムが、分子内のキノ

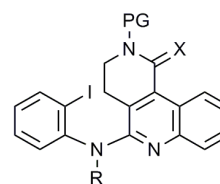
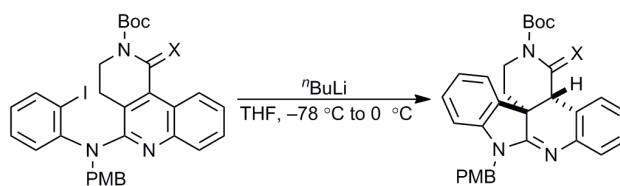


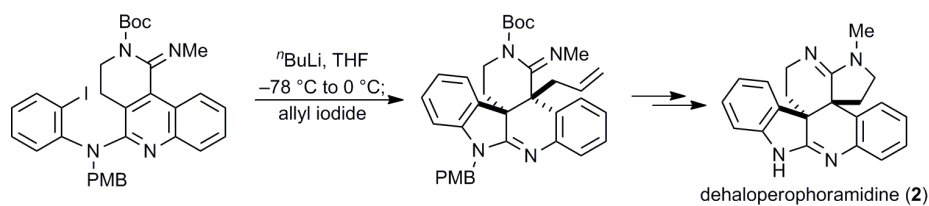
Figure 5. New Substrate

リン 3 位に付加する脱芳香族共役付加反応に基づいて設計された。実際にモデル化合物を合成して検討した結果、予想通り目的の脱芳香族共役付加反応が進行し、続くプロトン化によって **1** と同じ相対立体配置を有する五環性アミジンを一貫したジアステレオマーとして合成することに成功した (Scheme 12)。更に、本反応をビスアミジンに対して適用してワンポットでのアリル化を行うことで、所望の相対立体配置で二連続第四級炭素を有する五環性ビスアミジンを合成することができ、更に 4 工程を経てこの化合物から **2** へ誘導した (Scheme 13)。続いてハロゲン原子の導入について検討した結果、臭素原子を分子内に有するラクタム、加えて塩素原子を導入した基質であっても本反応が良好に進行することを見出し、更に反応によって得られたハロゲン化五環性ラクタムは、数工程を経て六環性ビスアミジンへと誘導することができた (Scheme

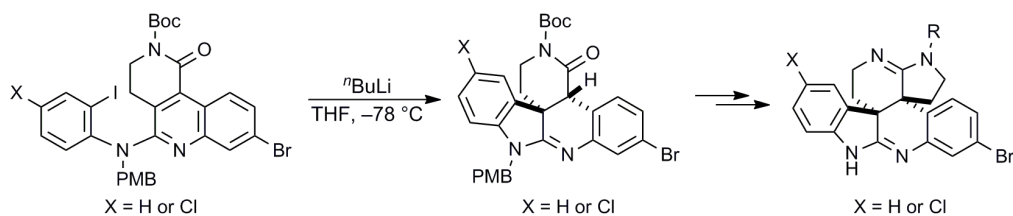


Scheme 12. Dearomatizing Conjugate Addition

14)。



Scheme 13. Construction of Contiguous All-Carbon Quaternary Centers and Synthesis of (±)-Dehaloperophoramidine



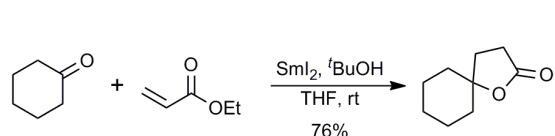
Scheme 14. Synthesis of Pentacyclic Lactam and Halogenated Hexacycle

第二章 ヨウ化サマリウム(II)による還元的環化反応を鍵反応とする骨格構築

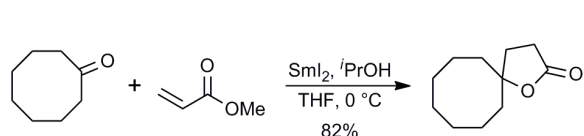
第一節 ヨウ化サマリウム(II)を用いた還元的環化反応の開発

1977年に Kagan らによって液相中での合成法が発見された¹⁹ことから Kagan 試薬とも称されるヨウ化サマリウム(II)(SmI_2)は、有機合成において様々な有用性が見出されてきた試薬の一つである。個々の詳細については書籍²⁰や総説²¹に譲るが、 SmI_2 が媒介する反応は、Barbier 型あるいは Grignard 型の付加反応、Reformatsky 反応、ラジカル付加反応、ヘテロ原子間、炭素原子間、炭素原子-ヘテロ原子間結合の開裂反応、カルボニル化合物の還元反応など幅広く知られており、天然物合成への応用も数多く報告されている。中でも、ピナコールカップリングに代表される電子求引基間の還元的な結合形成や、ラジカル付加反応によるケチル-オレフィンカップリングを可能とする点が SmI_2 の優れた特長の一つとしてあげられるが、本節では特に、電子求引基によって活性化された二重結合を反応点とする還元的炭素間結合形成反応(以下簡略に共役型ピナコールカップリング反応と称する)について紹介する。

1988年に Fukuzawa²²と Inanaga²³らによって独立して報告された還元的なブチロラクトン合成法が、 SmI_2 を利用した共役型ピナコールカップリング反応として知られる最初の例である (Schemes 15, 16)。いずれの報告においても、 SmI_2 とアルコールの存在下アルデヒドあるいはケトンが不飽和エステルとの反応によって良好な収率でラクトン環を形成することが述べられており、同文献内で Fukuzawa らは不飽和エステルからホモエノラートアニオン種が生成する可能性を残しながらも、本反応をケチルラジカルの付加反応によるものと考察した。

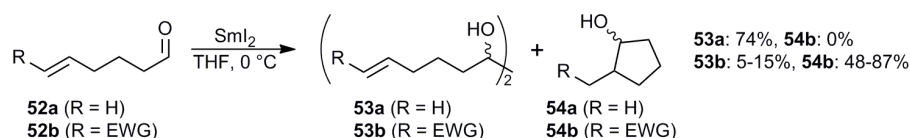


Scheme 15. Lactone Synthesis by Fukuzawa



Scheme 16. Lactone Synthesis by Inanaga

翌年の Enholm らの報告²⁴では分子内反応が検討されており、単純な末端オレフィンを有する基質からは分子間ピナコールカップリング生成物 **53** が優先するのに対し、電子求引基をもつ基質からは分子内共役型ピナコールカップリングが進行することが報告された (Scheme 17)。これによって反応経路に重要な役割を果たすことが示されるとともに、Fukuzawa らの検討では低収率に留まった不飽和ニトリルやアルケニルベンゼンが基質として適用可能であることが明らかにされた。

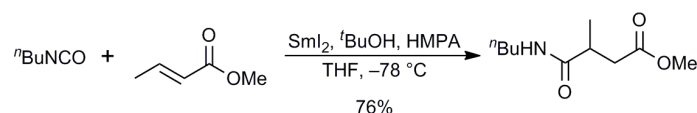


Scheme 17. Effect of EWG on Intramolecular Couplings Reported by Enholm

その後多くのアルデヒドまたはケトンと不飽和カルボニルとの共役型ピナコールカップリング

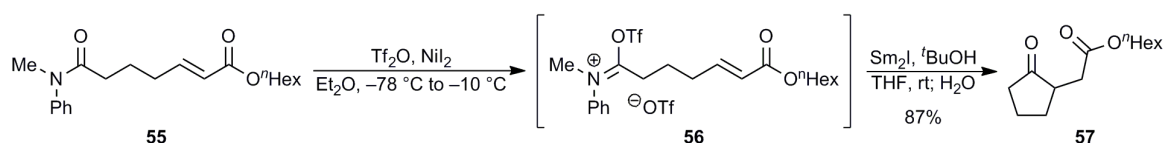
反応が報告され²⁵、また不斉反応への応用も精力的に研究されてきた²⁶。また、共役型ピナコールカップリング反応は官能基共存性に優れ、温和な条件下で高収率、高立体選択的に炭素間結合を形成できる特長を有しており、これらの利点から本反応はポリエーテル系天然物の環構築法をはじめとして、天然物の合成研究や全合成研究に数多く用いられた²⁷。

2000 年前後から、SmI₂ との反応性がよく知られているアルデヒドやケトンとは異なる官能基がカップリングに用いられる形で研究が展開された。1998 年に Kim らは、イソシアネートまたはイソチオシアネートと不飽和エステルの分子間還元的カップリング反応を報告した²⁸ (Scheme 18)。本反応では、*tert*-ブチルアルコールとヘキサメチルリン酸トリアミド (HMPA) の添加によって、良好な収率でアミドを得ることに成功している。



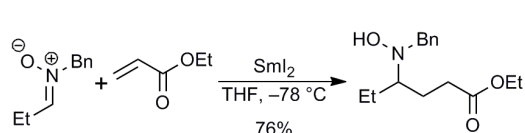
Scheme 18. Reductive Coupling of Isocyanates and Unsaturated Esters by Kim

2001 年の McDonald らによる報告では、分子内にアミドを有する不飽和エステル **55** にトリフルオロメタンスルホン酸無水物を作用させてイミニウム塩 **56** へと変換し、ヨウ化ニッケル (II) の存在下 SmI₂ による還元的環化反応を行って環状ケトン **57** が得られることが明らかにされた²⁹ (Scheme 19)。

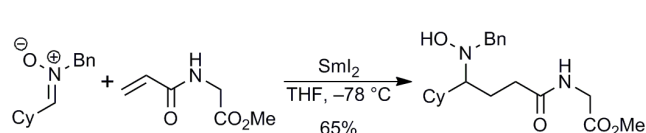


Scheme 19. McDonald's Reductive Cyclization of Amides and Unsaturated Esters via Iminium Triflates

2003 年に Py、Vallée らはニトロソと不飽和エステル^{30a}、Skrydstrup らはニトロソと不飽和エステルまたはアミド^{31a}との分子間還元的カップリング反応をそれぞれ報告した (Schemes 20,21)。いずれにおいても、系内の不斉点からのアミノ基 α 位への不斉誘起が検討され良好な選択性が確認されているが、特に Py らはその後本反応を γ -アミノ酸の不斉合成法へと展開^{30c}し、天然物合成への応用^{30b,d,e}についても報告している。



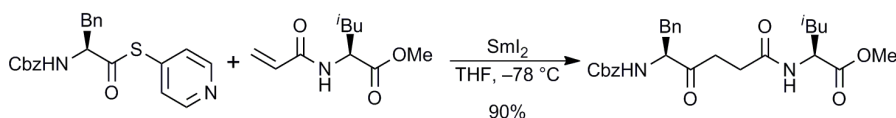
Scheme 20. Coupling of Nitrones by Py and Vallée



Scheme 21. Coupling of Nitrones by Skrydstrup

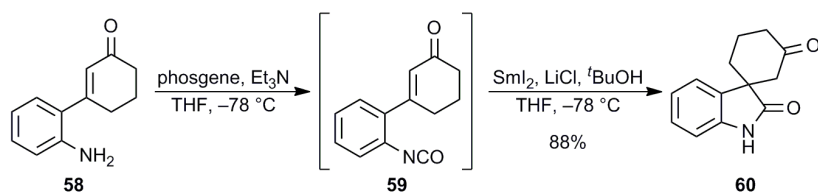
Skrydstrup らは同年に、チオエステルと不飽和エステルまたはアミドとの還元的カップリング反応を報告している^{32a} (Scheme 21)。本反応は、McDonald らの報告²⁹と同様にカルボン酸誘導体をアシルラジカル等価体として反応させるものであるが、特別な基質の活性化を必要とせず、アミ

ノ酸誘導体を原料に利用できる点を特長としている。また、後年に生物活性物質の合成への応用が報告された^{32b}。

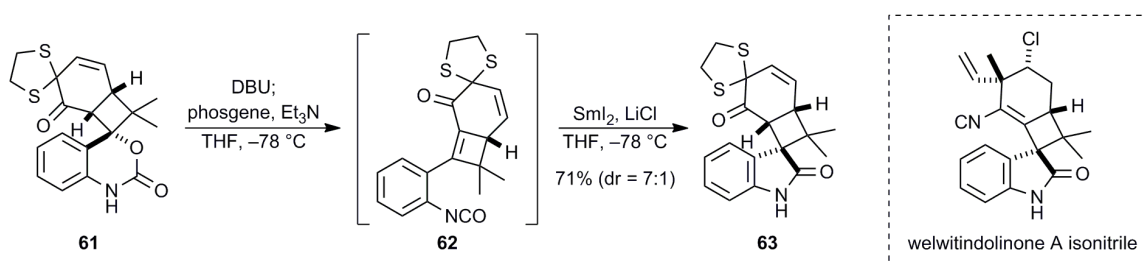


Scheme 22. Reductive Coupling of Thioesters and Unsaturated Amides by Skrydstrup

Wood らは、2001 年の Kim らによるイソシアネートの分子間還元的カップリングを分子内反応に適用することでスピロオキシインドールが合成できることを見出した^{33a}(Scheme 23)。アニリン **58** より合成したモデル基質 **59** による条件検討の結果、*tert*-ブチルアルコールに加えて塩化リチウムを添加することによって大幅な収率の改善が見られ、高収率で所望のスピロオキシインドール **60** が得られることが明らかとなり、更にカルバメート **61** より合成したイソシアネート **62** に対して適用することで良好なジアステレオ選択性で welwitindolinone A isonitrile の部分構造 **60** が構築された (Scheme 24)。後に、より高度に官能基化された基質 **61** に対して本反応が適用できることが示されたが welwitindolinone A isonitrile の全合成は異なる環化反応を用いて達成がなされている^{33b}。

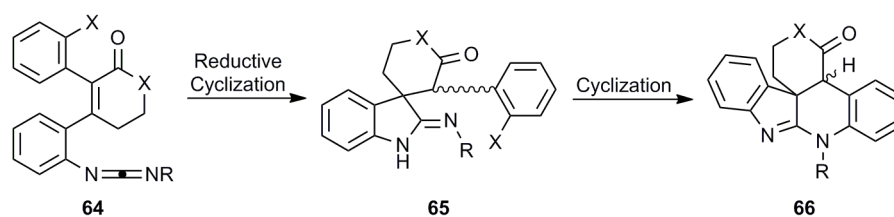


Scheme 23. Synthesis of Spirooxindole via Reductive Cyclization of Isocyanate by Wood



Scheme 24. Application to Construction of Core Structure of Welwitindolinone A Isonitrile

これまでに述べてきた通り Sml₂ による共役型ピナコールカップリング反応についてはこれまでに数多くの研究がなされてきたが、カルボジイミドを電子求引基として利用する反応例は報告されておらず、関連する研究としてもサマロセン誘導体によるホモカップリング反応³⁴が一例知られているのみであった。このような背景の下、Wood らによって報告されたオキシインドール合成法をカルボジイミド **64** に適用することで3位に第四級炭素を有する2-イミノインドリン合成法が開発できると想定し、この反応の生成物 **65** から更に環化を行うことで五環性アミジン **66** へ誘導できると考えた (Scheme 25)。



Scheme 25. Synthetic Strategy for Construction of Pentacyclic Core

五環性骨格構築後の上部アミジンへの官能基変換を考慮し、カルボジイミドを有する不飽和ラクタム (**Figure 6**) をモデル基質として設定し、その合成を行った (**Scheme 26**)。すなわち、市販のβ-アミノエステル **67** に対して塩化エチルマロニルを作用させて収率93%でアミド **68** とした後、Claisen

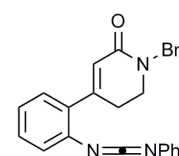
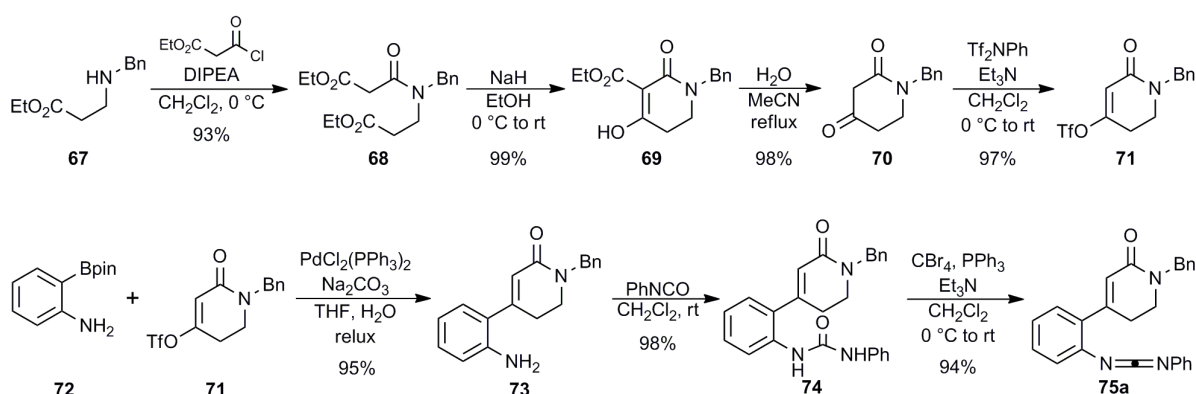


Figure 6. Model Substrate

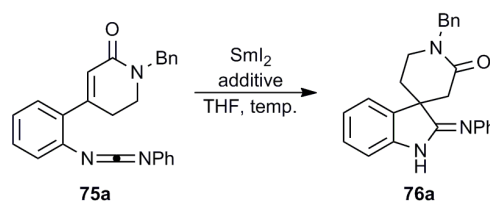
縮合によって収率99%で環化体 **69** を合成し、これを含水アセトニトリル中加熱還流することによってエステルの加水分解反応と脱炭酸反応が進行したβ-ケトラクタム **70**³⁵ を98%で得た。ラクタム **70** に対して *N*-フェニルビストリフルオロメタンスルホンイミド (Tf_2NPh)³⁶ を作用させて97%でアルケニルトリフラート **71** とし、Suzukiカップリング反応³⁷ によって既知のボロン酸エステル **72**³⁸ と結合させることでカップリング体 **73** を収率95%で合成した。フェニルイソシアネートを作用させて収率98%でウレア **74** へと変換し、トリフェニルホスフィンと四臭化炭素を用いた脱水反応によって所望のカルボジイミド **75a** を94%で合成した。



Scheme 26. Synthesis of Model Substrate

続いてカルボジイミド **75a** を基質として SmI_2 による還元的環化反応の検討を行った (**Table 1**)。テトラヒドロフラン (THF) 中でカルボジイミド **75a** に対して SmI_2 を 2.4 当量作用させると $-78\text{ }^\circ\text{C}$ では全く反応が進行しなかったが、室温条件下では反応が 15 分で完結し 55% で目的の環化体 **76a** を得ることができた (**Entries 1,2**)。なお、これらの反応は SmI_2 溶液に基質溶液を添加する逆添加条件にて実施した。続いて Fukuzawa²² や Inanaga²³ らの条件を参考にアルコールの添加を検討したところ、大過剰のメタノールあるいは 2.2 当量の *tert*-ブチルアルコールの添加によって収率の大幅な向上が見られ、それぞれ 82% と 83% の収率で目的物 **76a** を得た (**Entries 3,4**)。興味深いことに、

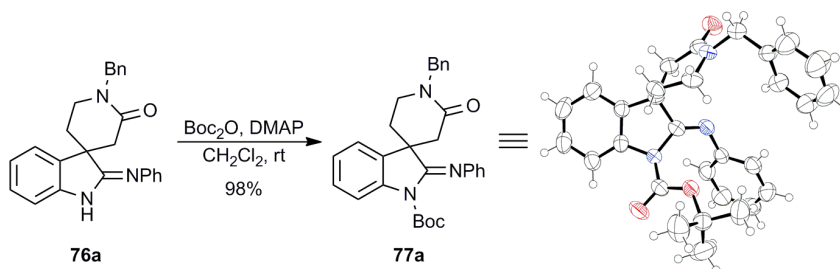
SmI₂ の還元電位を低下させることが知られている HMPA³⁹ の添加によっても収率の向上が見られたが (Entry 5)、*tert*-ブチルアルコールの共存下では若干の収率の低下が見られるのみであった (Entry 6)。その他、塩化リチウム^{40a,b} や臭化リチウム^{40a,b}、ヨウ化ニッケル^{40c} の添加を試みたが、いずれの条件においても、良好な収率で目的物が得られるものの収率の向上には至らなかった (Entries 7-9)。なお、生成物 76a のアミジンを Boc 基で保護した保護体 77a の構造は、X 線結晶構造解析によって決定した (Scheme



Entry	Additives	Temp.	Yield
1	none	-78 °C	0%
2	none	rt	55%
3	MeOH (50 eq.)	rt	82%
4	^t BuOH (2.2 eq.)	rt	83%
5	HMPA (10 %vol)	rt	78%
6	^t BuOH (2.2 eq.), HMPA (10 %vol)	rt	72%
7	^t BuOH (2.2 eq.), LiCl (10 eq.)	rt	68%
8	^t BuOH (2.2 eq.), LiBr (10 eq.)	rt	68%
9	^t BuOH (2.2 eq.), NiI ₂ (5 mol%)	rt	79%

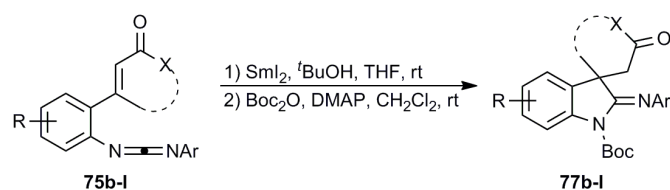
Table 1. Investigation of Reaction Conditions

27)。以上の検討結果から、室温で 2.2 当量の *tert*-ブチルアルコールを添加剤として加える条件を標準条件として、基質一般性の検討に移ることとした。



Scheme 27. Derivatization of Spiroiminodindoline

モデル基質 75a と同様の方法で合成した類縁体 75b-75j について、SmI₂ による還元的環化反応を検討した結果を次に示す (Table 2)。反応の生成物は重クロロホルム中でアミジンの互変異性体混合物として観測される場合があり、また一部の生成物では溶液中での経時的な分解が確認されたことから、基質一般性は還元的環化反応と生成物の Boc 保護による 2 工程の通算収率で評価することとした。モデル基質で良好な結果が得られた標準条件 (条件 A) で検討を行ったところ、後にインドリン環を構成する左側芳香環上の置換基については、カルボジイミドのパラ位メチル化体 75b、メトキシ化体 75c、クロロ化体 75d のいずれにおいてもそれぞれ 87%、73%、62% で目的の環化保護体 77a-c を、不飽和ラクタムのオルト位メトキシ化体 75e についても 75% と良好な収率で目的物 77e を得ることができた。続いて右側芳香環上の置換基について検討を試みたが、興味深いことに、初期に最適とされた条件 A では原因不明の全般的な収率の低下が見られる結果となった。ヘテロ原子、特にハロゲン原子を含む基質において顕著な収率の低下が見られたことから、①SmI₂ の調製に使用した金属サマリウム残渣が生成物と反応している、②反応で生じるサマ



Substrates	Products	Yield (A / B)*	Substrates	Products	Yield (A / B)*
		77b (R = Me) 87% / --- 77c (R = OMe) 73% / --- 77d (R = Cl) 62% / ---			65% / 86%
		75% / ---			77i (R = OMe) 46% / 74% 77j (R = F) 54% / 87%
		77f (R = OMe) 42% / 66% 77g (R = Cl) 45% / 86%			52% / 76%
					56% / 83%

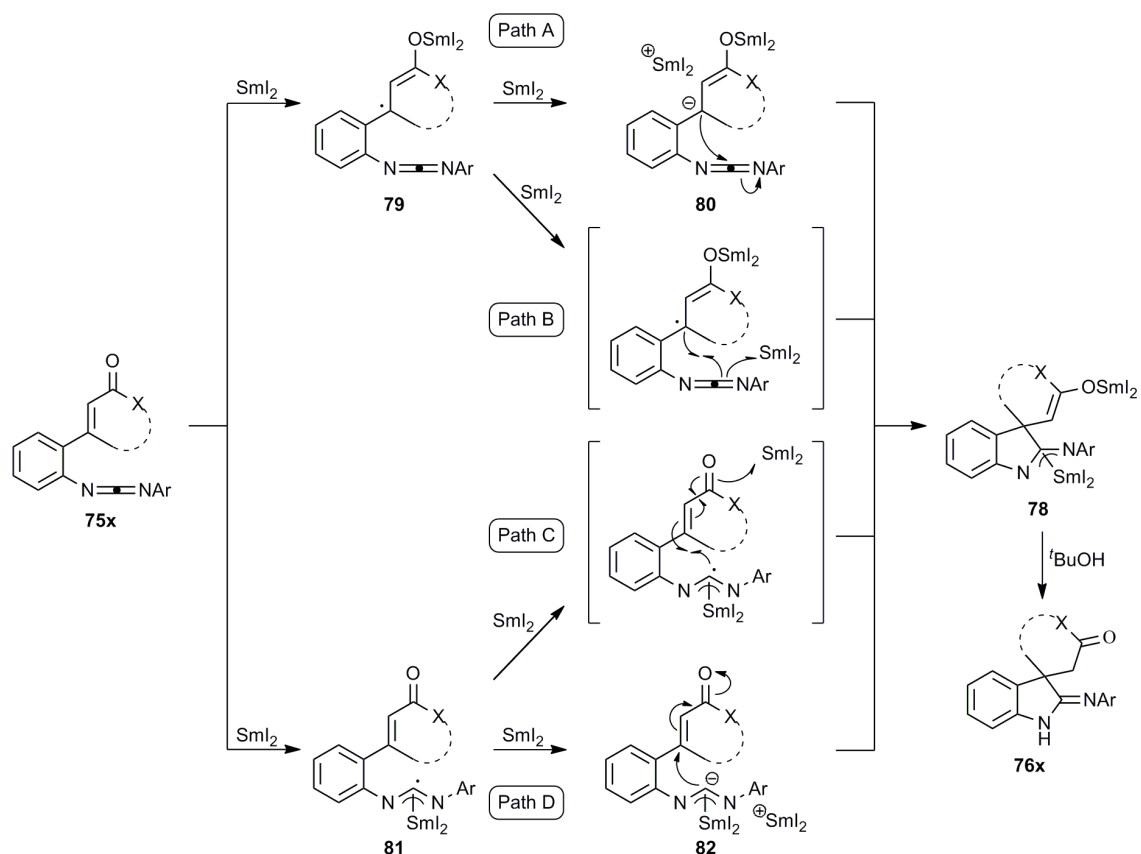
*A: Substrates and ^tBuOH (2.2 equiv.) in THF were added to SmI₂ (0.1 M in THF, 2.4 equiv).
 B: SmI₂ (0.1 M in THF, 2.1 equiv) was added to substrates and ^tBuOH (10 equiv.) in THF.

Table 2. Scopes and Limitations of Reductive Cyclization

リウムエノラートあるいはアミジネートが副反応を起こしているという二つの仮説を考え、これらに対応して反応条件を変更した。すなわち、金属サマリウムの介在を避けるために基質溶液への SmI₂ 溶液(上清)の添加を採用し、アニオン性中間体の迅速なプロトン化を意図して 10 当量の *tert*-ブチルアルコールを用いることで対処を試みた(条件 B)。条件 B で再度検討を行ったところ、目論見通り、全般的な収率の向上を確認することができた。カルボジイミドのオルト位にメチル基あるいはクロロ基をもつ基質 **75f,g** ではそれぞれ 66%、86%と良好な収率で環化保護体 **77f,g** が得られ、メタ位メチル化体 **75h**、パラ位メトキシ化体 **75i**、パラ位フッ素化体 **75j** についても 86%、74%、87%の収率でそれぞれ環化保護体 **77h-j** を得た。また、本反応はエステルに対しても適用可能であり、エステル **75k** とラクトン **75l** からそれぞれ 76%および 83%の収率で環化保護体 **77k,l** が得られ、ここでも条件の変更による収率向上が認められた。以上の検討によって、SmI₂ による還元的環化反応が各種の電子求引基および電子供与基を許容できる反応であることが示された。

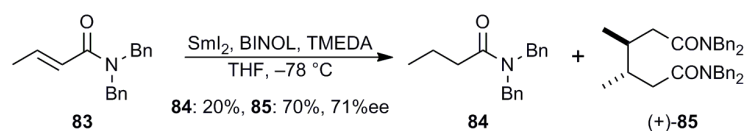
なお、不飽和カルボニルのβ位にアルキル置換基を持たない直鎖不飽和エステルまたはアミドは本反応に適さず、複雑な混合物が得られるのみであった。

シリカゲル薄層クロマトグラフィー (TLC) による反応の追跡から本反応の完結には 2 当量以上の SmI_2 が必須であることが明らかとなったため還元的環化には 2 当量の SmI_2 が関与していることが推察されるが、この反応の反応機構としては還元される部位と順序により大きく四つの候補が考えられる (Scheme 28)。基質 **75x** は SmI_2 による一電子還元を二度受けた後、アルコールによってプロトン化されることで最終的に環化体 **76x** へと変換される。プロトン化はいずれの段階でも可能ではあるが、仮にジアニオン **78** を最終中間体と仮定すると、四つの反応経路は以下の通りである。すなわち、①不飽和カルボニル部位が SmI_2 によって一電子還元を受けてラジカル **79** を生じた後、更に還元が起きてサマリウムホモエノラート **80** が生成し、これがカルボジイミドに対して付加反応を起こす経路 A、②ラジカル **79** がカルボジイミドに付加し、これを SmI_2 が捕捉することでジアニオン **78** に至る経路 B、③カルボジイミド部位に一電子還元が起きてラジカル **81** が生成した後、不飽和カルボニルβ位に付加し、生じたラジカルを SmI_2 が捕捉する経路 C、④ラジカル **81** が更に還元されてアニオン **82** へと変換された後に不飽和カルボニルβ位へ共役付加する経路 D の四つである。

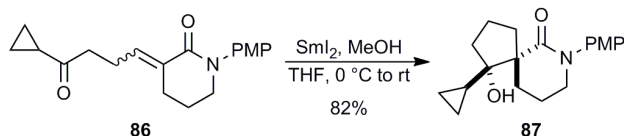


Scheme 28. Possible Reaction Pathways of Reductive Cyclization

不飽和アミドと SmI_2 の反応性については Inanaga⁴¹や Procter⁴²によって報告がなされている。すなわち、Inanaga らは大過剰量の BINOL と N,N,N',N' -テトラメチルエチレンジアミン (TMEDA) の存在下ではあるが、 $-78\text{ }^\circ\text{C}$ という低温下で N,N -ジアルキル不飽和アミド **83** が SmI_2 によって一電子還元を受けてラジカルを生じ、少量の共役還元体 **84** を伴いながら二量化体 **85** へと変換されることを報告した⁴¹ (Scheme 29)。また、Procter らの検討によって、 α 位に *exo* 型オレフィンをもつケトラクタム **86** が還元されることで分子内アルドール反応が進行し、スピロ環化体 **87** が得られることが明らかとなった⁴² (Scheme 30)。これらの知見は、不飽和ラクタムの還元を契機とする経路 A および B の可能性を強く示唆する結果であるといえる。なお、対照実験としてカルボジイミドを持たない不飽和ラクタム **75m** (Figure 7) を合成して還元的環化反応の条件を適用したところ、少量の複雑な混合物とともに 41% の原料が回収される結果となった。これは不飽和ラクタム部位と SmI_2 との反応性を示唆する結果であるとの解釈も可能ではあるが、その副生成物の構造が不明であるため明確な結論を導くことはできなかった。



Scheme 29. Reductive Dimerization of Unsaturated Amides by Inanaga



Scheme 30. Aldol Reaction of Unsaturated Lactam by Procter

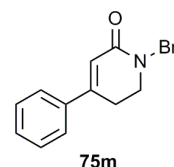
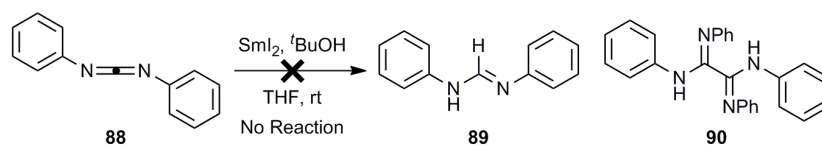
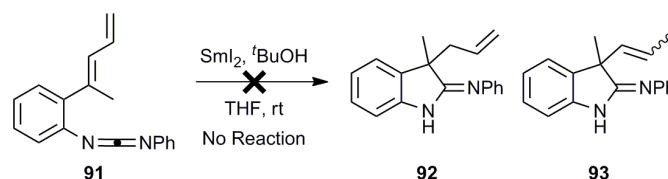


Figure 7. Substrate for Control

カルボジイミドと SmI_2 の反応性に関してはこれまでに同様の反応が全く報告されていなかったため、筆者は経路 C および経路 D の妥当性を検証すべく、類縁体を合成して対照実験を試みた (Schemes 31,32)。まず、ジフェニルカルボジイミド **88** に対して還元的環化反応の条件を適用したところ、一切反応が進行せず、還元体 **89** や二量化体 **90** は検出されなかった。この事実は、カル



Scheme 31. Reaction of Diphenylcarbodiimide under Reductive Cyclization Conditions

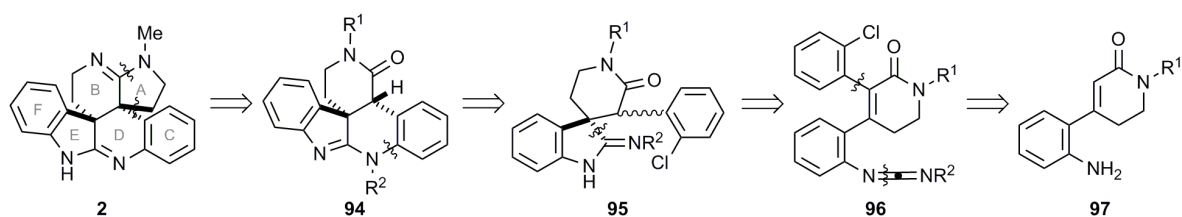


Scheme 32. Reaction of Dienyl Substrate under Reductive Cyclization Conditions

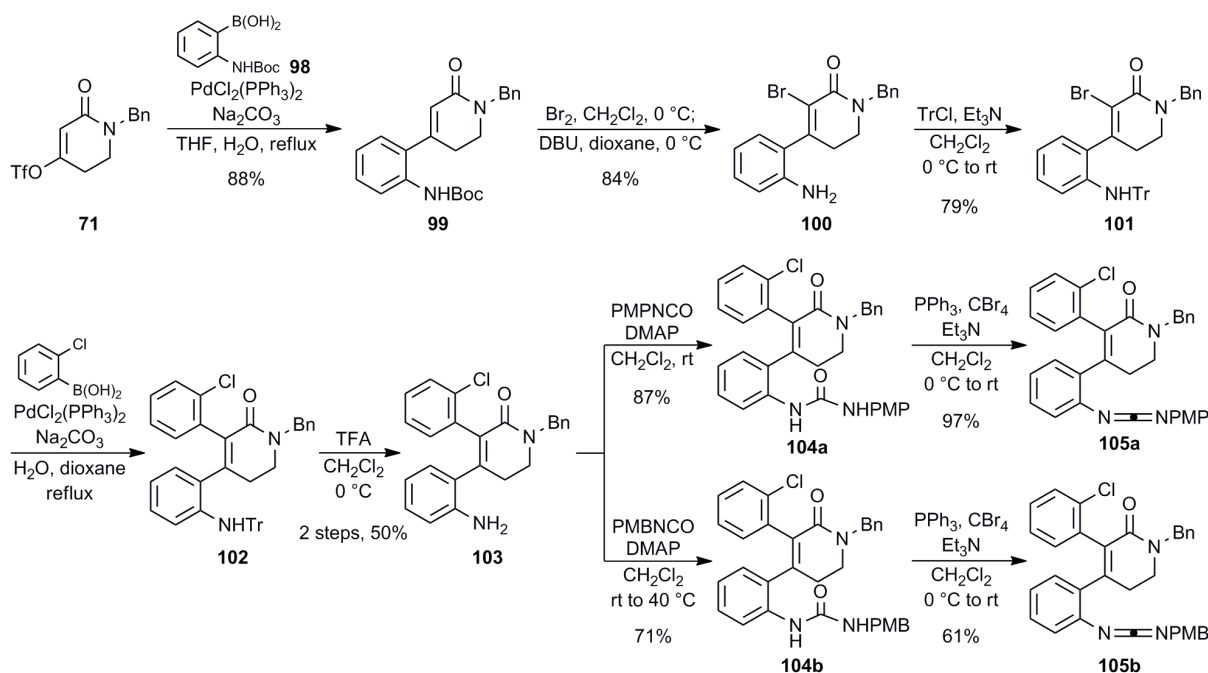
ボジイミドからジアニオン **82** を生成する経路 **D** を明確に否定する結果である。続いて、ラジカル受容体として分子内にジエンを持つカルボジイミド **91** で同様の検討を試みたが、こちらについても反応の進行は観察できず、環化体 **92** や **93** の生成は見られなかった。この結果は、アミジノイルラジカルの反応性が明らかでないため経路 **C** を明確に否定する結果ではないが、構造的に類似したイミドイルラジカル⁴³が不飽和結合に付加する事実を考慮すると経路 **C** に対して否定的な結果である。更なる検討の結果、本反応の進行はカルボジイミド上の置換基に大きく依存し、モノアルキルカルボジイミドを基質として用いた際には **HMPA** の添加が必須であった。**HMPA** 共存下での反応機構の同一性についてはより慎重な議論が必要となるものの、この結論は経路 **A** の妥当性に疑問を投げかけるものであると言える。この結果と議論の詳細については本章第二節で述べることとするが、以上の議論により本反応の反応経路としては経路 **B** が最も妥当であるとの結論に達した。

第二節 還元的環化反応による五環性アミジンの合成

前節で述べた SmI_2 による還元的環化反応に基づき、モデルとして dehaloperphoramidine (**2**) を標的化合物とした逆合成解析を行った (Scheme 33)。**2** の A 環を五環性ラクタム **94** から構築することとし、D 環を α 位に 2-クロロフェニル基を有するスピロラクタム **95** からの分子内環化反応によって形成することを計画した。スピロラクタム **95** のスピロイミノインドリンを、 SmI_2 による還元的環化反応によってカルボジイミド **96** から合成することとして、これに含まれる四置換オレフィンとカルボジイミドをアニリン **97** から構築することとした。

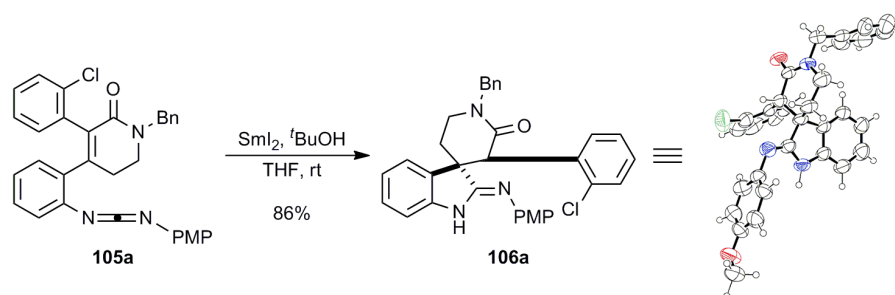


還元的環化反応の基質であるカルボジイミドは以下のように合成した (Scheme 34)。前述のビニルトリフラート **71** と既知のボロン酸 **98**⁴⁴ を Suzuki カップリング反応³⁷ によって結合し、収率 88% で Boc 保護アニリン **99** とした。これに対して臭素を作用させた後、溶媒の塩化メチレンと余剰の臭素を減圧留去して溶媒をジオキサンに置換し、1,8-ジアザビシクロ[5.4.0]ウンデ-7-セン (DBU) を作用させると α 位のブロモ化と Boc 基の除去が進行したアニリン **100** を 84% の収率で得ることができた。アニリン **100** の窒素原子をトリチル基で保護して 79% の収率で保護体 **101** とした後、



2-クロロフェニルボロン酸を鈴木カップリング反応で結合することで四置換オレフィンを有するラクタム **102** を合成し、粗生成物をトリフルオロ酢酸で処理することでアニリン **103** を2工程50%の収率で得た。これに対して対応するイソシアネートを作用させて、収率87%および71%で *N'*-(*p*-メトキシフェニル)(PMP)ウレア **104a** および *N'*-(*p*-メトキシベンジル)(PMB)ウレア **104b** へと変換し、トリフェニルホスフィンと四臭化炭素を用いた脱水反応によってカルボジイミド **105a,b** をそれぞれ収率97%と61%で合成した。

基質一般性検討の結果良好な結果が得られた *N,N'*-ジアリールカルボジイミド **105a** について SmI_2 による還元的環化反応の条件を適用したところ、単一のジアステレオマーとして環化体 **106a** を86%の収率で得ることができた (Scheme 35)。生成物 **106a** の構造はX線結晶構造解析により決



Scheme 35. Reductive Cyclization of Aryl Lactam

定したが、その結果二つの芳香環が互いに *cis* 配置を取っていることが明らかとなった。この選択性の発現機構については、立体障害のためにインドリン環側からのサマリウムエノラート **107** へのプロトン化が妨げられ、その結果としてアミジン側からのプロトン化が優先したためと考えられる (Figure 8)。続いて筆者は *N'*-PMB 体 **105b** について同様の反応を試みた (Table 3)。興味深いことに、還元的環化反応の最適条件では全く反応が進行せず、原料が未反応のまま回収される結果となった (Entry 1)。反応系を60℃まで加熱しても効果がなく同様の結果に終わったが (Entry 2)、HMPA を添

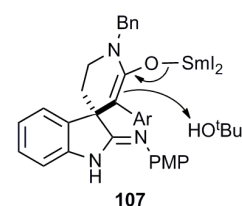
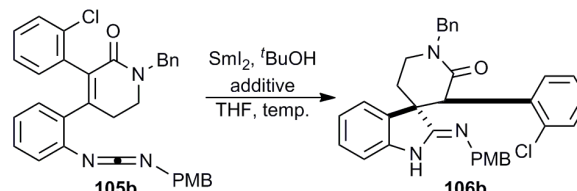


Figure 8. Diastereoselective Protonation

加すると反応は室温でも進行し、目的の環化体 **106b** を90%と優れた収率で得ることができた (Entry 3)。

ここで得られた、カルボジイミド上の置換基による反応性の差異と HMPA の添加による反応の促進効果に関する知見は極めて興味深い。HMPA の添加によって反応



Entry	Additive	Temp.	Results
1	none	rt	No Reaction
2	none	60 °C	No Reaction
3	HMPA (5%vol)	rt	90%

Table 3. Reductive Cyclization of PMB-Substituted Carbodiimide

機構が変化しないと仮定すると、ジアリールカルボジイミドにおける還元的環化反応の経路 A (Scheme 26) の妥当性には疑問の余地がある。すなわち、不飽和ラクタムから 2 当量の SmI_2 による一電子還元を受けて生成したホモエノラート **108** (Figure 9) が、モノアルキルカルボ

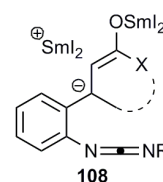
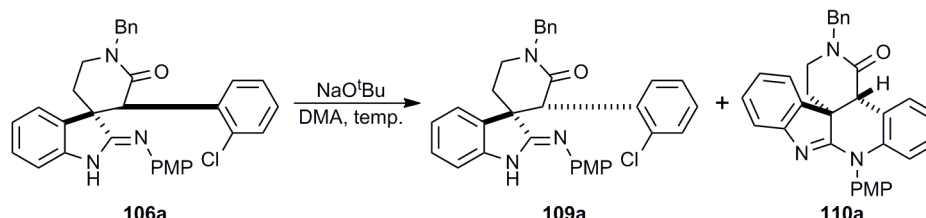


Figure 9. Homoenolate Dianion

ジイミド ($\text{R}=\text{PMB}$) に対して付加するために HMPA が必要とされることになる。HMPA は SmI_2 の還元電位を下げる役割が知られている Lewis 塩基³⁹であり、求電子剤であるカルボジイミドの活性化に寄与するとは考えにくい。Lewis 塩基としてホモエノラート側の求核性を向上させている可能性は否定できないが、テトラヒドロフラン中 60 °C まで加熱しても、HMPA の非存在下で反応しないホモエノラートが過剰量存在する *tert*-ブチルアルコールによってプロトン化を受けないことは妥当性に乏しい。一方、前節の議論から示唆される経路 B では、HMPA が SmI_2 の還元電位を下げることで、電子豊富なアルキル置換基の影響で還元されにくくなったカルボジイミドの一電子還元を可能にしていると解釈すれば矛盾は生じない。以上の推論から、本章第一節で検討した還元的環化反応の反応機構はホモエノラート (経路 A) を経由しないことが示唆される。

目的の還元的環化反応が進行したことで、 α 位にアリール基を有するスピロラクタム **106a,b** が得られたが、その相対配置は perophoramidine とは異なるものであったため、ラクタム α 位の異性化が解決すべき課題の一つであった。そこで筆者は、塩基を用いた異性化反応を検討することとした (Table 4)。スピロラクタム **106a** に対してジメチルアセトアミド (DMA) 中、3 当量のナトリウム *tert*-ブトキシドを作用させて 24 時間攪拌したところ、室温では反応が進行しなかったが (Entry 1)、60 °C に加熱した場合には 45% の原料回収とともに 20% の異性体 **109** が得られた (Entry 2)。更に昇温して 120 °C とすると、異性体 **109a** の他に少量ながら生成物が確認され、解析の結果所望の五環性アミジン **110a** であることが明らかとなった。目的物 **110a** の相対立体配置は NOESY スペクトルにおいてラクタム α 位のプロトンと芳香環上の二つのプロトンに NOE が観測されたことから決定した (Figure 10)。遷移金属の添加なしに環化の進行が見られたが、これにはいくつかの候



Entry	Temp.	Result
1	rt	No Reaction
2	60 °C	106a : 45%, 109a : 20%
3	120 °C	106a : 11%, 109a : 5%, 110a : 27%

Table 4. Isomerization Experiments

補となる反応機構が考えられる。主要なものは①芳香族求核置換の反応機構、②アリアルラジカルを経由する反応機構、③ベンザインを経由する反応機構の三つであるが、その詳細については明らかとなっていない。

五環性アミジン **110a** の収率は 27% と十分ではなかったが、筆者はこの結果から、ラクタム α 位の異性化を伴いながら D 環が構築できる可能性を

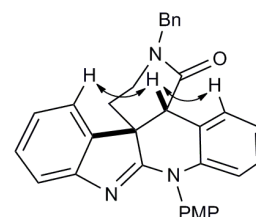


Figure 10. Observed NOE

を見出し、塩基存在下でのパラジウム触媒による環化反応⁴⁵の検討に着手した (Table 5)。パラジウム触媒として酢酸パラジウム 10 mol% を添加し、塩化アリールに対する酸化的付加において高い活性をもたらすことが知られているアルキルホスフィン を 20 mol% 添加して DMA 中 120 °C で 24 時間加熱する条件で検討した結果、触媒と配位子を添加しない条件 (Entry 1) に比べて cataCXium[®] A^{46a} を用いた場合にはほとんど収率が変化しなかったが (Entry 2)、トリ *tert*-ブチルホスフィン^{46b} テトラフルオロホウ酸塩を添加した場合には 63% まで大幅な収率の改善が見られた (Entry 3)。更にシクロヘキシル基を持つホスフィンは概して良好な結果を与え、CyclohexylJohnPhos^{46c} では 66%、DavePhos^{46d} では 70% とそれぞれ収率の向上が見られた (Entries 4,5)。特にトリシクロヘキシルホスフィン^{46e,f} テトラフルオロホウ酸塩は高い活性を示し、17 時間で原料の消失とともに 78% で目的の環化体 **110a** を得ることができた (Entry 6)。反応の進行に伴って系内にパラジウム黒の形成が認められたため、これを抑制する目的で触媒と配位子の添加量を半減して反応を試みたところ、同じく 17 時間で反応が完結し、86% と優れた収率で目的物 **110a** を得るに至った (Entry 7)。

Entry	Pd(OAc) ₂	Ligand (mol %)	Time	Yield
1	none	none	24 h	27%
2	10 mol %	cataCXium [®] A (20)	24 h	31%
3	10 mol %	<i>t</i> Bu ₃ P·HBF ₄ (20)	24 h	63%
4	10 mol %	CyclohexylJohnPhos (20)	24 h	66%
5	10 mol %	Davephos (20)	24 h	70%
6	10 mol %	Cy ₃ P·HBF ₄ (20)	17 h	78%
7	5 mol %	Cy ₃ P·HBF ₄ (10)	17 h	86%

106a → **110a**

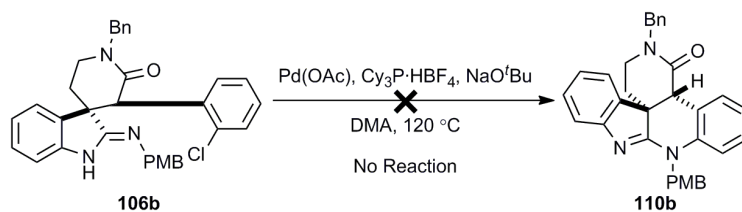
cataCXium[®] A
CyclohexylJohnPhos
(R = H)

DavePhos
(R = Me₂N)

Table 5. Synthesis of Pentacyclic Lactam via Pd-Catalyzed Cyclization

以上に述べたように、筆者は独自に見出した Sml₂ による還元的環化反応を高度に官能基化された基質に対して適用して目的のスピロイミノインドリンを合成し、続く環化反応で異性化を伴いながら五環性アミジン骨格に誘導することができた。しかしながら、アミジン上の PMP 基の除去が困難な課題であり、酸化的条件を適用すると基質の分解が競合する結果となった。これに対処

すべく、PMB 基をアミジン上の保護基として持つ **106b** を基質として、最適化されたパラジウム触媒による環化反応を適用したが、目的の五環性アミジン **110b** が得られることはなく原料回収に終わった (**Scheme 36**)。環化反応が進行しない原因としては、置換基の変更によってアミジンの性質、特に塩基性や配位能が大きく変わっており、ホスフィン配位子の活性に強く依存する本反応を阻害したものと考えられる。残念ながら、この結果を受けて筆者は第一世代の合成戦略の実施を断念することとした。



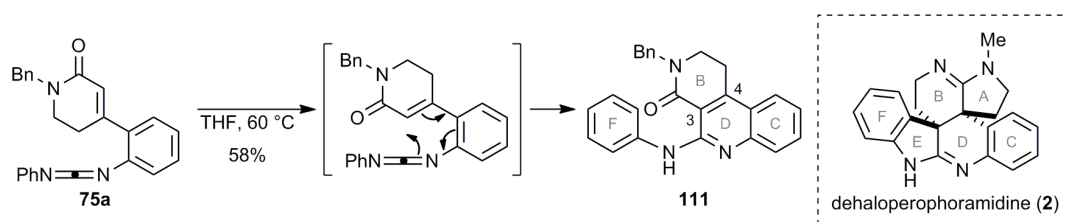
Scheme 36. Unsuccessful Cyclization of PMB-Substituted Iminoindoline

第三章 脱芳香族共役付加反応を鍵反応とする骨格構築

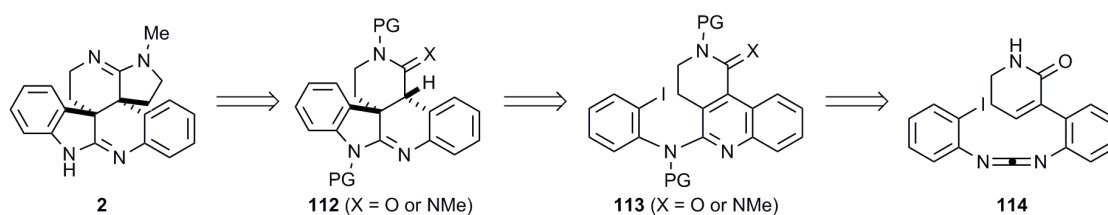
第一節 脱芳香族共役付加反応の開発とデハロペロフォラミジンの合成

前章で述べた骨格構築法の開発では、概ね良好な収率で五環性アミジン **110a** が得られたものの、いくつかの課題が浮き彫りとなった。すなわち、①下部アミジンの保護基が除去困難な *p*-メトキシフェニル (PMP)基に限定されていたこと、②各ユニットの連結および D 環の構築にパラジウム触媒による結合形成反応を利用したため最終的なハロゲン原子、特に臭素原子の導入が困難であると考えられること、③β-アミノ酸 **67** から五環性アミジン **110a** までに 13 工程、既知化合物である β-ケトラクタム **70**³⁵ から同化合物までに 10 工程と多段階を要していること、④四置換オレフィン **103** の合成が条件最適化後も比較的低収率に留まったことである。このうち、①および②は D 環構築のための環化反応に起因する一方で、②-④の問題点は全て四置換オレフィンの形成に関与するものであった。

ところで、ヨウ化サマリウム (II) (SmI₂)による還元的環化反応のモデル基質 **75a** は室温条件下において若干の不安定性を有していることが観察され、その利用には化合物の用時調製が必須であった。その副反応は熱的な 6π 電子環状反応であり、特に加熱条件下ではアミノキノリン **111** が 58%と中程度の収率で得られることが明らかとなった (Scheme 37)。このような 6π 電子環状反応による 2-アミノキノリン合成法は Saito^{47a}、Molina^{47b} らによってそれぞれ独立に報告されたものであったが、アミノキノリン **111** は dehaloperophoramidine (**2**)の六環性骨格のうち B-D 環および F 環を既に有しており、更にキノリンの 3,4 位炭素-炭素結合は潜在的な四置換オレフィンとして利用できる可能性があった。



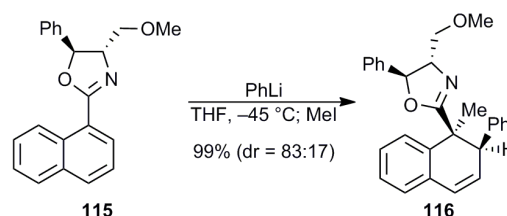
これらの知見をもとに、筆者は次の合成戦略を考案した (Scheme 38)。まず、**2** の A 環をアミドあるいはアミジンをもつ五環性アミジン **112** から構築することとした。この五環性アミジン **112** の第四級炭素は、アミノキノリン **113** に対してリチウム-ヨウ素交換反応によって分子内にアリールリチウムを生成させ、これをキノリン 3 位に共役付加させることで構築できると考えた。この 2-アミノキノリン **113** は、ラクタムを有するカルボジイミド **114** から先述の 6π 電子環状反応と、続く保護および官能基変換によって合成することとした。



Scheme 38. Retrosynthetic Analysis of Dehaloperophoramidine

本合成戦略において重要な役割を果たす脱芳香族共役付加反応は、電子求引基によって活性化された 10π 電子芳香族系に対する有機リチウムの付加によって第四級炭素を構築する点を特徴としている。脱芳香化を伴う合成法は、比較的容易に合成できる芳香族化合物から複雑な構造を構築できる点で合成効率の高い反応として広く研究がなされてきたが⁴⁸、その中でも本研究に関連する報告例としてはナフタレン誘導体に対する有機リチウム試薬の付加反応が挙げられる。

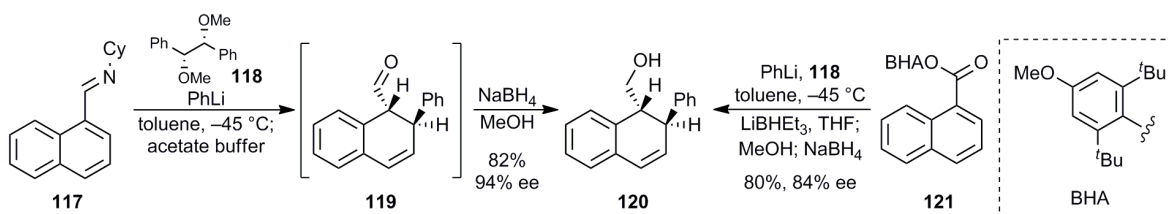
Meyers らは 1984 年に、不斉補助基をもつ環状イミデート **115** に対して有機リチウム試薬を作用させ、生じたアザエノラートを求電子剤で捕捉することでジアステレオ選択的に脱芳香族共役付加体 **116** が得られることを報告し^{49a} (Scheme



Scheme 39. Dearomatizing Conjugate Addition by Meyers

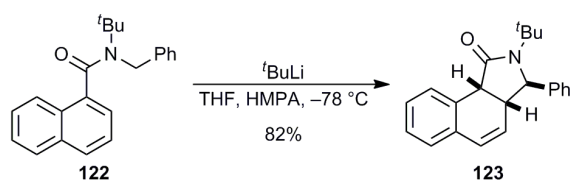
39)、その後本反応についての幅広い検討を行っている⁴⁹。

また、Tomioka らはイミン **117** に対するフェニルリチウムの付加反応が少過剰量の光学活性ジエーテル配位子 **118** によってエナンチオ選択的に進行し、アルデヒド **119** への加水分解と、続く還元反応を経てアルコール **120** が高収率、高エナンチオ選択的に得られることを報告した^{50a} (Scheme 40)。後年には、嵩高い置換基を用いることでエステル **121** からも同様の反応が進行することが報告されている^{50b-e}。

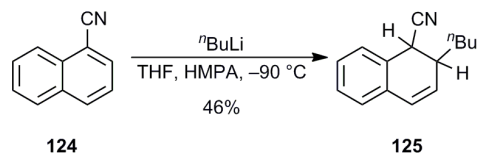


Scheme 40. Tomioka's Enantioselective Dearomatizing Conjugate Addition using Chiral Diether Ligand

Clayden らは *N*-ベンジルナフタミド **122** に *tert*-ブチルリチウムを作用させることでベンジル位あるいは芳香環オルト位のリチオ化が進行し、ヘキサメチルリン酸トリアミド (HMPA) の存在下で脱芳香族環化反応が進行した生成物 **123** が得られることを見出し (Scheme 41)^{51a,b}、後に不斉補助基を利用した不斉合成法へと展開した^{51c}。また Ortiz らはシアノナフタレン **124** へのアルキルリチウムの付加反応による共役付加体 **125** の合成について報告している (Scheme 42)⁵²。

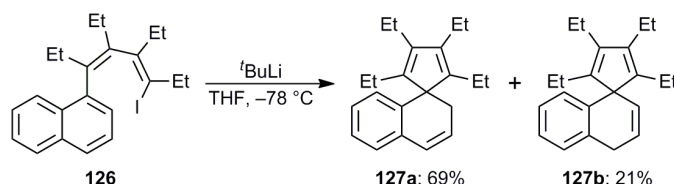


Scheme 41. Intramolecular Cyclization by Clayden



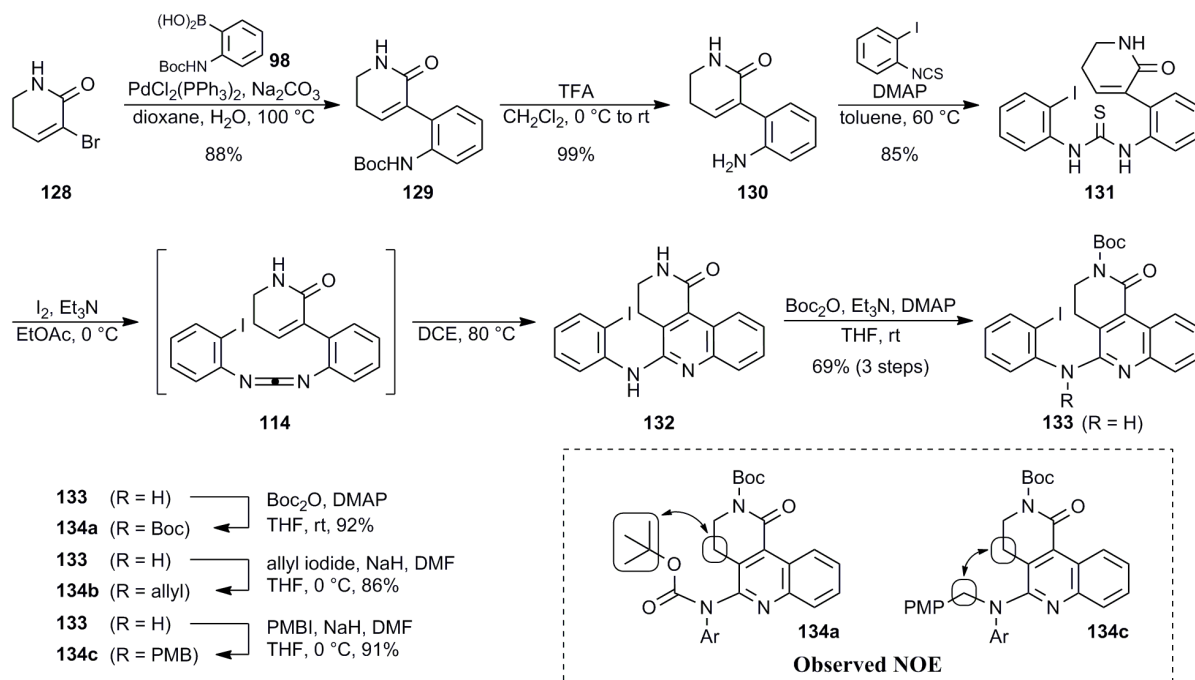
Scheme 42. Addition to Cyanonaphthalene by Ortiz

以上は 10π 電子芳香族系化合物への脱芳香族共役付加反応の代表的な例であり、反応の結果生じる(アザ)エノラートを求電子剤で捕捉することによって電子求引基の α 位を第四級炭素に変換する手法もそれぞれについて報告されている。しかしながら、分子内反応あるいは分子間反応を問わず、求核付加を受ける電子求引基 β 位を第四級炭素に変換する同様の共役付加反応はこれまで知られておらず、関連する研究としても Xi らによる単純なナフタレン **126** へのアニオン環化反応によるスピロ環化体 **127a,b** の合成のみであった (Scheme 43)⁵³。また、キノリンあるいはイソキノリンを基質とする類似の反応も未開拓の分野であった。



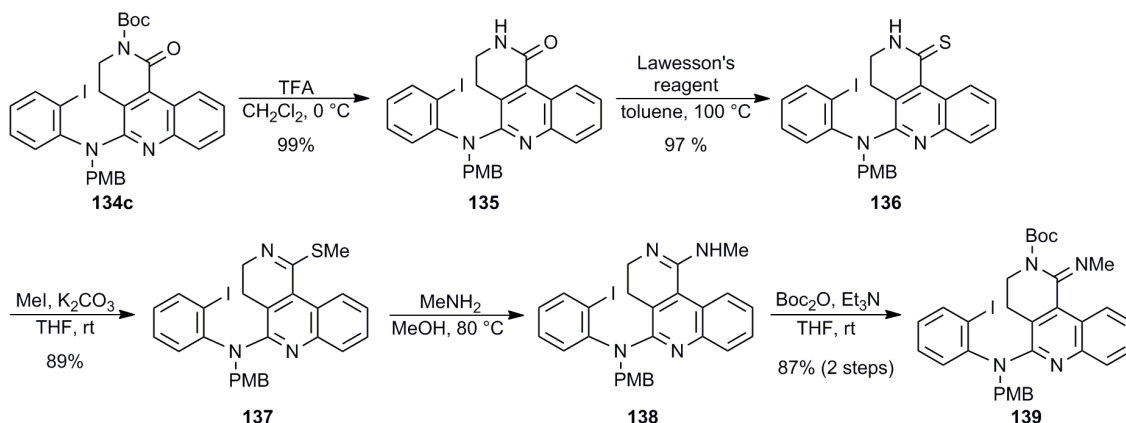
Scheme 43. Dearomatizing Anionic Cyclization by Xi

以上の背景を踏まえ、筆者は仮説を検討すべくモデル基質の合成を行った (Scheme 44)。文献既知のラクタム **128**⁵⁴とボロン酸 **98**⁴⁴を鈴木カップリング反応によって結合して Boc 保護アニリン **129** を収率 88%で合成し、Boc 基をトリフルオロ酢酸 (TFA)によって除去して 99%でアニリン **130**とした。これに 2-ヨードフェニルイソチオシアネートを作用させて 85%でチオウレア **131**を合成した後、ヨウ素を用いた脱硫反応⁵⁵によってカルボジイミド **114**へと変換し、これを単離することなくジクロロエタン中 $80\text{ }^\circ\text{C}$ で加熱することによって所望のアミノキノリン **132**を粗生成物として得た。続いてラクタム窒素原子を選択的に Boc 基で保護することによって、3 工程 69%収率で Boc 保護ラクタム **133**へ誘導した。次に、アミノキノリン **133**を Boc 基で更に保護することで Boc 化体 **134a**を、アリル化および *p*-メトキシベンジル (PMB)化することによってアリル化体 **134b**、PMB 化体 **134c**をそれぞれ 92%, 86%, 91%の収率で合成した。このうち Boc 化体 **134a**および PMB 化体 **134c**については、NOESY スペクトル上で図中の NOE が観測されたことから官能基化は環外窒素選択的に進行しているものと判明した。なお、興味深いことに **133**のアルキル化反応にはアルキル化剤としてヨウ化アルキルが必須であり、PMBCl や臭化ベンジルを用いた官能基化はいずれも良好な収率で目的物を与えなかった。



Scheme 44. Synthesis of Aminoquinoline Substrates

続いてモデル基質 **134c** を更に誘導化することで、アミドをアミジンへ変換したアミノキノリンを合成した (Scheme 45)。まず、アミノキノリン **134c** の Boc 基を TFA によって収率 99% で除去してアミド **135** とし、ここから Lawesson 試薬⁵⁶ によってチオラクタム **136** を 97% の収率で得た。続いて、ヨウ化メチルを用いた *S*-メチル化によって収率 89% でメチルチオイミデート **137** とし、メチルアミンで置換することでアミジン **138** へと変換後、Boc 基による保護を経て 2 工程 87% の収率で Boc 保護アミジン **139** を合成した。



Scheme 45. Synthesis of Amidine Derivative

このように合成したアミド **134a-c** およびアミジン **139** を基質として、脱芳香族共役付加反応の検討を行った (Table 6)。テトラヒドロフラン (THF) 中 -78 °C において基質に対して 1.1 当量の *n*-ブチルリチウム (*n*BuLi) を作用させて 0 °C まで昇温して 1 時間攪拌する条件を初期条件としたところ、Boc 保護体 **134a** は原料の消失と共に複雑な混合物を与えたのに対し (Entry 1)、アリル保護体

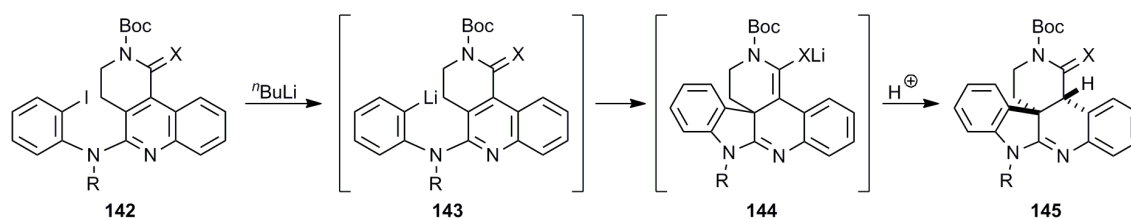
Entry	Substrates	X	R	ⁿ BuLi	Temp.	Results
1	134a	O	Boc	1.1 eq.	-78 °C to 0 °C	decomp.
2	134b	O	allyl	1.1 eq.	-78 °C to 0 °C	140b : 68%
3	134c	O	PMB	1.1 eq.	-78 °C to 0 °C	140c : 63%
4	134c	O	PMB	2.1 eq.	-78 °C to 0 °C	140c : 68%
5	139	NMe	PMB	1.1 eq.	-78 °C to 0 °C	140d : 41%, 141 : 23%, 139 : 12%
6	139	NMe	PMB	1.6 eq.	-78 °C to 0 °C	140d : 57%, 141 : 6%
7	139	NMe	PMB	2.1 eq.	-78 °C to 0 °C	140d : 74%, 141 : trace
8	139	NMe	PMB	2.1 eq.	-78 °C	140d : 28%, 141 : 46%
9	139	NMe	PMB	2.1 eq.	0 °C	140d : 40%, 141 : trace

Structure of **140d**
by X-ray Crystallography

Table 6. Investigation of Dearomatizing Conjugate Addition

134b および PMB 保護体 **134c** を用いた場合には目的の五環性ラクタム **140b** および **140c** をそれぞれ 68%と 63%の収率で得ることができた (Entries 2,3)。また、PMB 保護体 **134c** に対して作用させる ⁿBuLi を 2.1 当量に増量した場合にも目立った副反応は観察されず、68%と同程度の収率で目的の環化体 **140c** が得られた (Entry 4)。これに対してアミジン **139** は異なる反応性を示し、初期条件 (1.1 当量)においては 41%と低収率の五環性ビスアミジン **140d** に加え、23%の脱ヨウ素化体 **141** と 12%の原料が回収される結果となった (Entry 5)。ⁿBuLi の量を漸増させると、原料の消失および脱ヨウ素化体の減少と共に目的物の収率向上が見られ、1.6 当量では 57%、2.1 当量では 74%の収率でそれぞれ目的のビスアミジン **140d** を得ることができた (Entries 6,7)。このアミジン体 **139** の脱芳香族共役付加反応は-78 °Cあるいは 0 °Cでは良好に進行しないことから、-78 °Cでの試薬の添加とその後の昇温が高収率に必須であることが明らかとなった (Entries 8,9)。なお、生成物であるビスアミジン **140d** の構造は X 線結晶構造解析によって決定され、その結果 B 環上の 2 つの芳香環が互いに *trans* 配置である perophoramidine と同じ相対配置をもつことが明らかとなった。

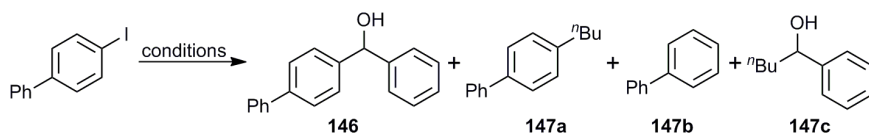
本反応の推定反応機構を次に示す (Scheme 46)。リチウム-ハロゲン交換反応によってヨウ化アリール **142** から有機リチウム **143** が生成し、これが分子内のキノリン 3 位へ 5-*exo* 型の脱芳香族共役付加反応を起こすことで(アザ)エノラート **144** を生じ、プロトン化を経て生成物 **145** に至る。



Scheme 46. General Mechanism of Dearomatizing Conjugate Addition

アミド **134c** の場合とは対照的に、アミジン **139** を基質とした際に $^n\text{BuLi}$ の添加量が収率に影響している事実は興味深い知見である。アミドを電子求引基とする脱芳香族共役付加反応は昇温を必要とせず $-78\text{ }^\circ\text{C}$ でも進行する事実(本章二節で詳述)、更にアミジン **139** に 1.1 および 1.6 当量の $^n\text{BuLi}$ を作用させた場合の副生成物が脱ヨウ素化体 **141** であった点を考慮すると、余剰の $^n\text{BuLi}$ はリチウム-ハロゲン交換反応の副生成物であるヨウ化ブチル (^nBuI) のスカベンジャーとして働くことが推察される。すなわち $-78\text{ }^\circ\text{C}$ での環化反応が遅いために系内に蓄積したアリールリチウム **143** に対して、副生した ^nBuI からのプロトン化反応が昇温過程で競合したと考えられる。

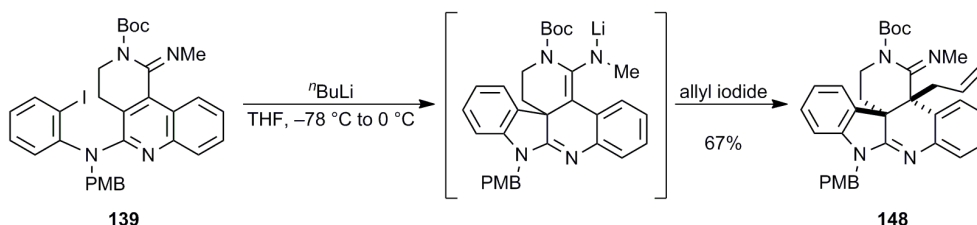
余剰の $^n\text{BuLi}$ の役割を確認すべく次の実験を試みた (Table 7)。THF 中、4-ヨードビフェニルに対して $-78\text{ }^\circ\text{C}$ にて 1.0 当量の $^n\text{BuLi}$ を作用させて $0\text{ }^\circ\text{C}$ まで昇温すると、4-ブチルビフェニル **147a**⁵⁷ が 94% の収率で得られ、プロトン化体であるビフェニル **147b** は観察されなかった (Entry 1)。これに対して同様の条件下 2.0 当量の $^n\text{BuLi}$ を作用させ、昇温後に 2.2 当量のベンズアルデヒド (PhCHO) を添加した場合、14% のプロトン化体 **147b** と共に PhCHO 付加体 **146**⁵⁸ が 73% と良好な収率で単離され、 $^n\text{BuLi}$ の PhCHO 付加体 **147c** は得られなかった (Entry 2)。続いて $-78\text{ }^\circ\text{C}$ における反応性を確認すべく同様の検討を行った。 $-78\text{ }^\circ\text{C}$ で 1.0 当量の $^n\text{BuLi}$ を作用させて 1 時間攪拌し、1.1 当量の PhCHO を添加した後に $0\text{ }^\circ\text{C}$ まで昇温すると、72% の PhCHO 付加体 **147c** に伴って、ブチル化体 **147a** やプロトン化体 **147b** がそれぞれ 9% ずつ得られる結果となった (Entry 3)。2.0 当量の $^n\text{BuLi}$ を用いて 2.2 当量の PhCHO を添加した場合、PhCHO 付加体 **147c** のみが 89% の収率で単離された (Entry 4)。これらの実験から次の事実が明らかである。①リチウム-ハロゲン交換反応の結果生じたアリールリチウム種は ^nBuI と副反応を起こす。②この副反応は $-78\text{ }^\circ\text{C}$ では遅いが $0\text{ }^\circ\text{C}$ ではアリールリチウムが速やかに消費される。③余剰の $^n\text{BuLi}$ が存在した場合、これが消費されることで前述の副反応は抑制される。④余剰の $^n\text{BuLi}$ の消費は $-78\text{ }^\circ\text{C}$ においても速やかに進行する。これらの知見は ^nBuI の役割についての仮説を裏付けるものであるが、脱芳香族共役付加反応での副反応がアルキル化ではない原因は不明であり、反応過程で分子内の脱プロトン化によってアリールリチウムとは異なる化学種が生成している可能性も考えられる。



Entry	Conditions	Results
1	$^n\text{BuLi}$ (1.0 eq.), THF, $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	147a : 94%, 147b : 0%
2	$^n\text{BuLi}$ (2.0 eq.), THF, $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$; PhCHO (2.2 eq.)	146 : 73%, 147a : 0%, 147b : 14%, 147c : 0%
3	$^n\text{BuLi}$ (1.0 eq.), THF, $-78\text{ }^\circ\text{C}$; PhCHO (1.1 eq.), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	146 : 72%, 147a : 9%, 147b : 9%, 147c : 0%
4	$^n\text{BuLi}$ (2.0 eq.), THF, $-78\text{ }^\circ\text{C}$; PhCHO (2.2 eq.), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$	146 : 89%, 147a-c : 0%

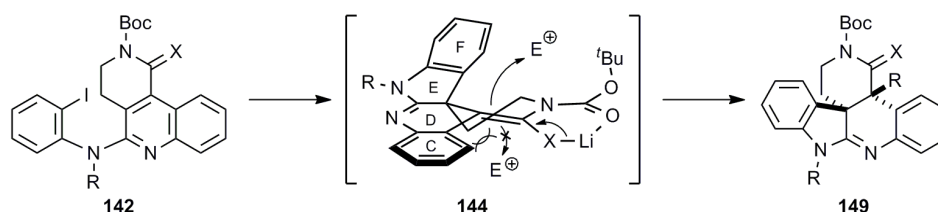
Table 7. Investigation of Effects of Excessive $^n\text{BuLi}$

続いて筆者は、得られた五環性ビスアミジン **140d** の上部アミジン α 位の修飾を試みた。しかしながら、塩基としてリチウムジイソプロピルアミド (LDA) やカリウムヘキサメチルジシラジド (KHMDS)、アリル化剤としてヨウ化あるいは臭化アリルを用いた場合には目的物が低収率で得られるのみであった。これはアルキルアミジンの α 位プロトンの引き抜きが困難であることに由来していると考えられたことから、筆者は脱芳香族共役付加反応の中間体であるアザエノラートをワンポットで修飾し、二連続第四級炭素を一挙に構築すべく検討を試みた。アミジン **139** の最適条件 (Table 6, Entry 7) を適用した後に 2.1 当量のヨウ化アリルを添加すると、67% と良好な収率で二連続第四級炭素を備えた五環性ビスアミジン **148** を得ることができた (Scheme 47)。なお、本反応の生成物も単一のジアステレオマーとして得られたが、これを最終的に **2** に変換することができた事実から、アリル化体 **148** は望みの相対立体配置を有していることが明らかである。



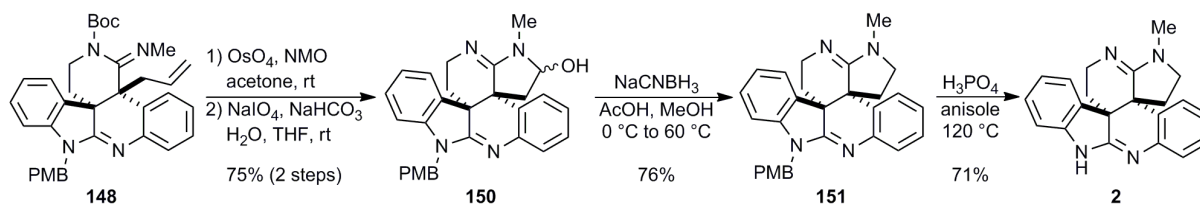
Scheme 47. One-Pot Construction of Contiguous All-Carbon Quaternary Centers

本反応のジアステレオ選択性は以下のように説明される (Scheme 48)。基質 **142** に対してリチオ化反応と脱芳香族共役付加反応が進行した (アザ)エノラート中間体 **144** は、下部アミジンの sp^2 混成によって C から F 環までの高い平面性が保たれる結果として、イミノインドリン 3 位に結合したエチレン側鎖はそれに直交することになる。プロトンやヨウ化アリルのような求電子剤の接近に対して、このアルキル側鎖が立体障害として機能することで生成物 **149** の立体選択性が発現していると推測される。



Scheme 48. Rationale for Diastereoselectivity

生成物 **148** から **2** への変換は以下のように行った (Scheme 49)。N-メチルモルホリン-N-オキシド(NMO)を代替酸化剤とする四酸化オスミウムによるジヒドロキシル化と、続く過ヨウ素酸ナトリウムによる酸化分解によってビスアミジン **148** の末端オレフィンを実アルデヒドへ変換したところ、分子内環化と同時にアミジン上の Boc 基が除去された六環性アミン **150** を 3:2 のジアステレオ比、75%の収率で得た。このヒドロキシル基をシアノ水素化ホウ素ナトリウムによって還



Scheme 49. Completion of Synthesis of Dehaloperophoramidine

元して収率 76%でビスアミジン **151** へと変換し、リン酸-アニソール溶媒中 120 °C で加熱することで PMB 基を除去⁵⁹して収率 71%で dehaloperophoramidine (**2**)の合成を達成した。なお、トリフルオロ酢酸を添加した重クロロホルム中で測定した **2** の ¹H および ¹³C 核磁気共鳴スペクトルは、Ireland らによって報告されているもの¹とよい一致を示した (Figure 11)。

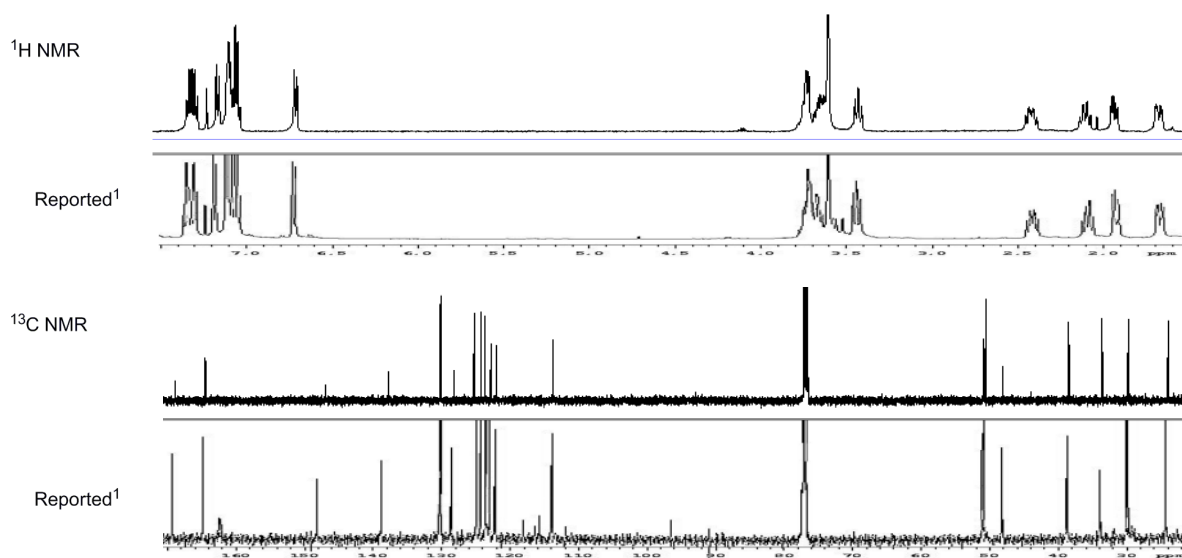


Figure 11. Comparison of NMR Spectra of Dehaloperophoramidine

本研究における **2** の合成経路は文献既知化合物であるブロモラクタム **128**⁵⁴ から 17 工程、その通算収率は 9.5%であり、既に報告されている Rainier らの合成経路² (*N*-ベンジルトリプタミンより 18 工程、総収率 7.5%)よりも合成工程数が少なく、また高収率であった。

第二節 脱芳香族共役付加反応によるハロゲン化六環性ビスアミジンの合成

前節の結果を受け、筆者は perophoramidine (1) に含まれる 8 位の臭素原子、15 位および 17 位の塩素原子の導入に着手することとした (Figure 12)。脱芳香族共役付加反応の基質合成経路において F 環が終盤に導入される点、ならびにアニリンのオルト位およびパラ位の塩素原子は求電子的塩素化反応によって導入できる点を考慮し、8 位臭

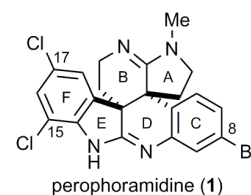
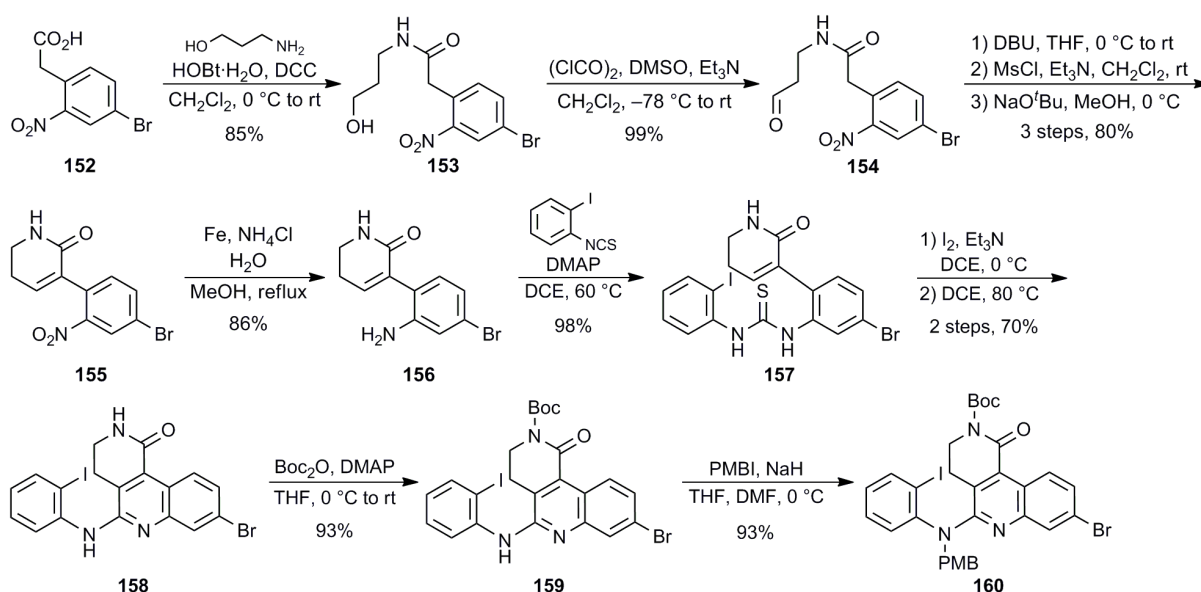


Figure 12. Structure of Target

素原子の導入を第一に解決すべく基質合成経路を検討した。前節で述べた合成経路では① α -プロモラクタム 128 の合成はジメチルホルムアミド(DMF)中低濃度で行われ、反応後に DMF の留去を必要とする点でスケールアップに限界があった点、②ボロン酸 98 に対応する臭素化有機金属試薬の合成法が確立されていなかった点、③鈴木カップリング反応を基盤とする合成法では導入した臭素への副反応が懸念される点を理由として、臭素化体の合成は抜本的に異なる合成法に基づいて行うこととした。

臭素を導入した基質の合成経路を次に示す (Scheme 50)。市販原料から 2 工程で合成できる文献既知のカルボン酸 152⁶⁰と 3-アミノ-1-プロパノールを 1-ヒドロキシベンゾトリアゾール (HOBt) 一水和物存在下、ジシクロヘキシルカルボジイミド (DCC) によって縮合して収率 85% でアミド 153 とし、これを Swern 酸化⁶¹によって収率 99% でアルデヒド 154 へと変換した。1,8-ジアザビシクロ [5.4.0]ウンデ-7-セン (DBU) を塩基とする分子内アルドール反応の後、ヒドロキシル基のメシル化とナトリウム *tert*-ブトキシドによる脱離反応を経て、アルデヒド 154 を 3 工程通算 80% の収率で不飽和ラクタム 155 とし、更に金属鉄によるニトロ基の還元によって収率 86% でアニリン 156 を



Scheme 50. Synthesis of Brominated Aminoquinoline

合成した。前節で述べた合成法に従い、臭素を導入したアニリン **156** から収率 98%でチオウレア **157** とし、ここから 70%の収率でアミノキノリン **158** を得た。更に収率 93%で Boc 保護ラクタム **159** へと変換し、PMB 化することで 93%の収率でキノリン 7 位に臭素を導入したアミノキノリン **160** を合成することができた。

得られたアミノキノリン **160** を基質として脱芳香族共役付加反応を試みた (Table 8)。THF 中、 $-78\text{ }^{\circ}\text{C}$ にて 2.1 当量あるいは 1.1 当量の $^n\text{BuLi}$ を 2 分間かけて添加した後 1 時間反応させたところ、いずれも 78%の収率で目的の臭素化五環性ラクタム **161** を得ることができた (Entries 1,2)。種々検討の結果、 $^n\text{BuLi}$ の添加時間が収率に大きく影響することが明らかとなり、1.1 当量の $^n\text{BuLi}$ を 5 分間かけて添加することで収率は 90%まで向上した (Entry 3)。生成物 **161** の構造は X 線結晶構造解析によって決定し、本反応がキノリン 7 位の臭素原子をよく許容することが示された。

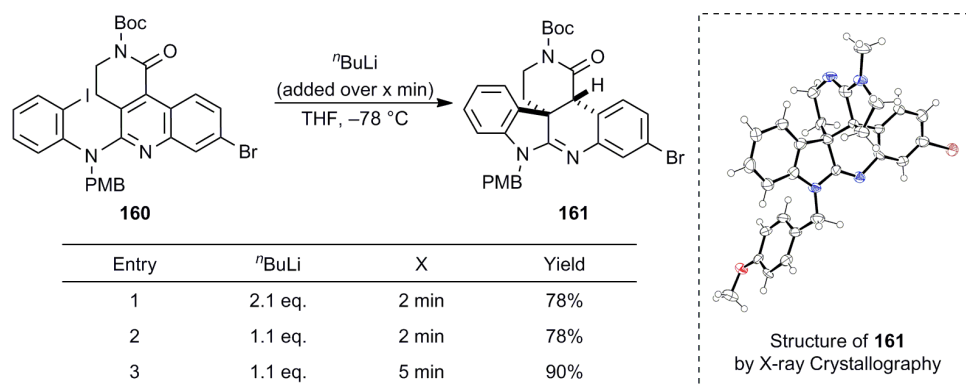
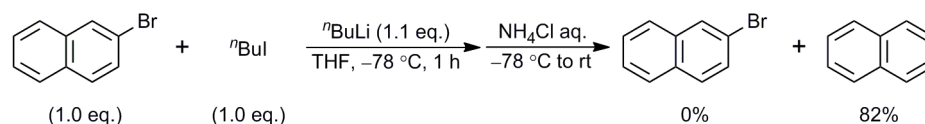


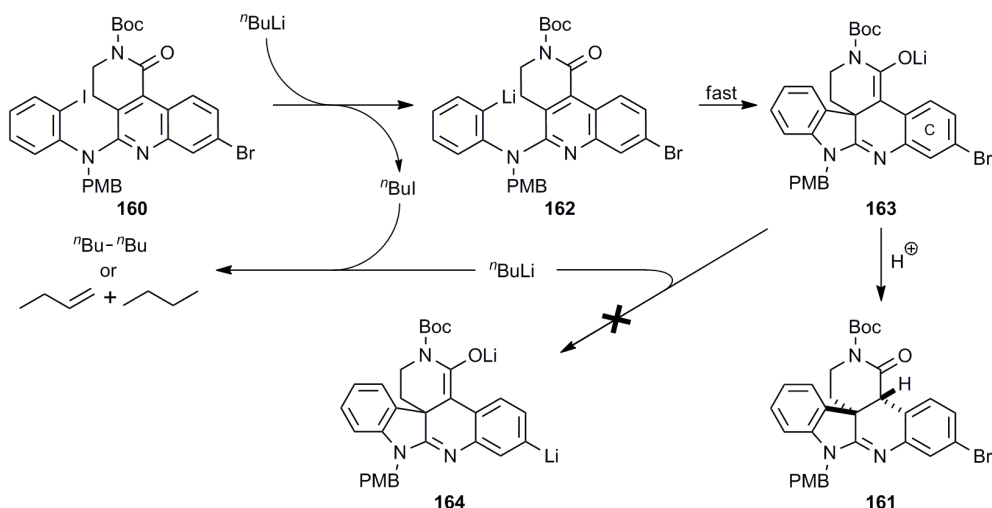
Table 8. Dearomatizing Conjugate Addition of Brominated Substrate

ヨウ化アリールが臭化アリールに優先してリチウム-ハロゲン交換反応を受けることは関連文献から明らかであったものの⁶²、脱芳香族共役付加反応において添加する $^n\text{BuLi}$ の当量に依らず臭素原子が許容される点は興味深い。 $^n\text{BuLi}$ を 2.1 当量添加した場合での余剰の $^n\text{BuLi}$ は、副生した ^nBuI と反応して消費されているものと考えられるが、この現象の一般性についての知見を得るべく次の実験を行った (Scheme 51)。モデル化合物として 2-ブロモナフタレンを原料とし、1.0 当量の ^nBuI 共存下、THF 中 $-78\text{ }^{\circ}\text{C}$ にて 1.1 当量の $^n\text{BuLi}$ を添加して 1 時間反応させた後、飽和塩化アンモニウム水溶液を添加して室温まで昇温したところ、原料はすべて消費され、脱臭素化が進行したナフタレンが 82%の収率で得られる結果となった。明らかに生成物はリチウム-臭素交換反応の結果生じるナフチルリチウムのプロトン化反応によって生成しており、この結果から $-78\text{ }^{\circ}\text{C}$ における臭化アリールの $^n\text{BuLi}$ に対する反応性は ^nBuI よりも優れていることが示唆される。従って、



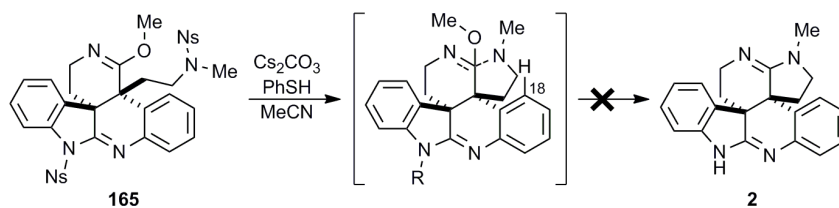
Scheme 51. Model Experiment on Reactivity of Aryl Bromide

2.1 当量の $n\text{BuLi}$ 存在下で臭素が許容される現象は、副生する $n\text{BuI}$ による $n\text{BuLi}$ の消費のみでは説明できない。臭素化された基質における脱芳香族共役付加反応の全体像は以下のようなものである (Scheme 52)。アミノキノリン **160** は、 $n\text{BuLi}$ によるヨウ素選択的なリチオ化を受けて有機リチウム **162** へと変換され、更に分子内の電子不足なアミノキノリン 3 位に速やかに 5-*exo* 型で付加してエノラート **163** となる。エノラート **163** は前節で述べた立体選択性に基づいてプロトン化を受けて生成物 **161** を与えるが、反応系の余剰の $n\text{BuLi}$ はこのエノラート **163** に対しては反応性を示さず、系内に副生した $n\text{BuI}$ と反応してオクタンないしブタンとして消費される。エノラート **163** が第二のリチウム-ハロゲン交換反応を受けない理由は明らかではないが、共役系によって C 環に電子供与を起こすモノアニオンであるために生成物であるジアニオン **164**、あるいはこれに至る反応経路の遷移状態が特に不安定化されている可能性が考えられる。



Scheme 52. Overview of Dearomatizing Conjugate Addition of Brominated Substrate

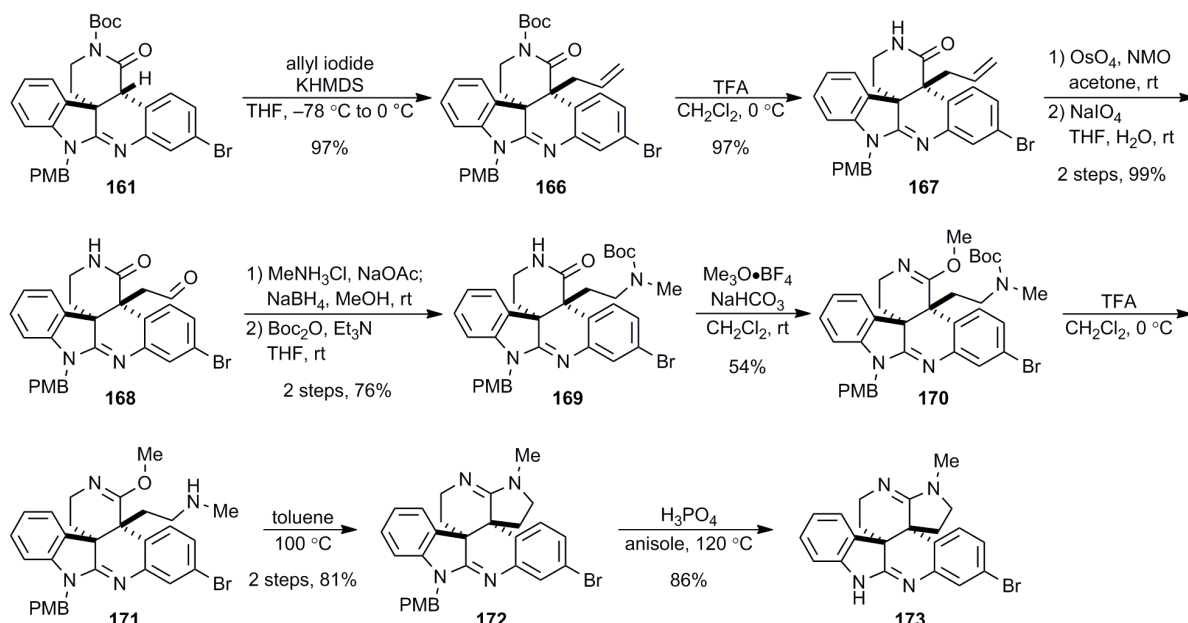
続いて筆者は、得られた五環性ラクタム **161** から A 環の構築を行って六環性ビスアミジンへの誘導を試みた。第 1 章 2 節末尾でも述べたが、dehaloperphoramidine (**2**)の合成を報告した Rainier らは下部アミジンを有するラクタム **165** からの A 環の構築について検討しており、脱ノシル化の条件において環化体 **2** が得られなかった実験事実から、本反応が進行しない理由を 18 位水素の立体障害に帰している² (Scheme 53)。更に、先行研究である Funk らが下部アミナルを有する基質で同様の反応を成功させている点を鑑み、Rainier らは下部アミナルの開環が A 環構築に重要な



Scheme 53. Unsuccessful Cyclization and Proposed Rationale by Rainier

役割を果たしていると推察した (Scheme 9)。しかしながら、分子模型モデルでの検討から筆者は A 環の構築における 18 位水素の立体障害は深刻ではなく、加熱による分子の活性化によって十分克服可能ではないかと予想し、この仮説の検証に着手することとした。

脱芳香族共役付加反応によって得られた臭素化五環性ラクタム **161** から以下のように A 環の構築を試みた (Scheme 54)。ラクタム **161** の α 位をヨウ化アリルと KHMDS によってアリル化して収率 97% でアリルラクタム **166** とし、TFA によって Boc 基を除去して脱保護体 **167** を 97% で得た。*N*-メチルモルホリン-*N*-オキシド (NMO) を代替酸化剤とする四酸化オスmiumによるジヒドロキシル化と、続く過ヨウ素酸ナトリウムによる酸化分解によってアルデヒド **168** を収率 99% で合成した後、メチルアミン塩酸塩を用いた還元的アミノ化と Boc 化によって収率 76% で Boc 保護アミン **169** とした。Meerwein 試薬によってラクタム酸素原子をメチル化して収率 54% でメチルイミデート **170** へと変換し、更に TFA によって Boc 基を除去することでアミン **171** を粗生成物として得た。このアミン **171** をトルエン中 100 °C で加熱したところ、筆者の目論見通り、2 工程 81% と良好な収率で目的の環化体 **172** を得ることができた。この環化体 **172** はリン酸-アニソール溶媒中で加熱して PMB 基を除去することによって収率 86% で 8 位臭素化ビスアミジン **173** へと変換した。



Scheme 54. Construction of A Ring and Synthesis of Brominated Hexacyclic Bisamidine

脱芳香族共役付加反応の臭素原子許容性を確認した筆者は、続けて 15 位および 17 位塩素原子の導入に着手した。合成したビスアミジン **173** から直接的に塩素化体を得る良好な条件が見出せなかったため、次に、鍵反応の基質であるアミノキノリンへの塩素原子導入を検討することとした。しかしながら理想的なジクロロ化イソチオシアネート **174** (Figure 13) の合成が困難であったため、まずアニリン部位へパラ位の塩素を導入してアミノキノリンを構築し、その後オルト位に

クロロ化を行う二段階で基質のジクロロ化を行うこととした。

アミノキノリンへの塩素化と脱芳香族共役付加反応の検討結果を次に示す (Scheme 55)。先と同様に、4-クロロ-2-ヨードフェニルイソチオシアネートを用いてアニリン **156** から収率 99%でチオウレア **175**

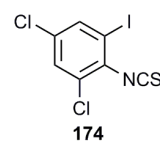
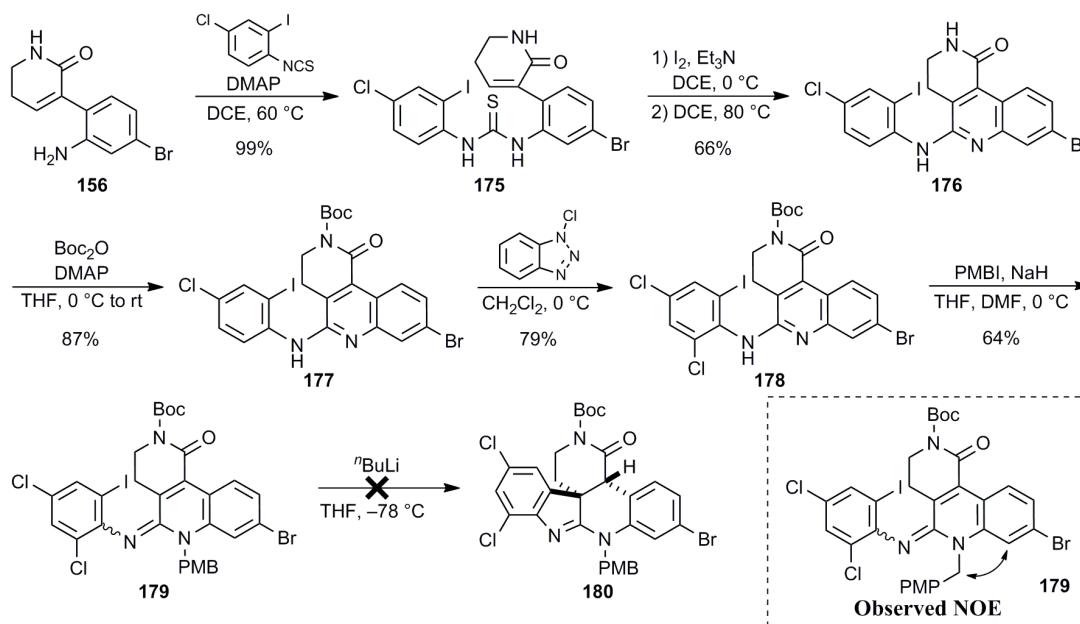


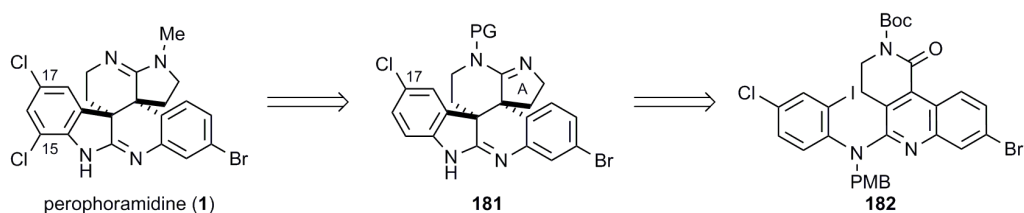
Figure 13. Ideal Isothiocyanate

を合成し、2工程 66%でアミノキノリン **176** とした後、収率 87%で Boc 保護ラクタム **177** を合成した。検討の結果、1-クロロベンゾトリアゾールを作用させることでアニリンのオルト位を選択的にクロロ化でき、収率 79%でジクロロ化アミノキノリン **178** が得られたが、これに対する PMB 化反応はキノリン環内窒素原子選択的に進行することが NOESY スペクトルの分析から明らかとなった。残念ながら、収率 64%で得られた PMB 化体 **179** からは脱芳香族共役付加反応による環化体 **180** の生成は観察されず、主に *n*-ブチル基の付加体が含まれる複雑な混合物が得られるのみであった。



Scheme 55. Synthesis of Dichlorinated Substrate and Attempt of Dearomatizing Conjugate Addition

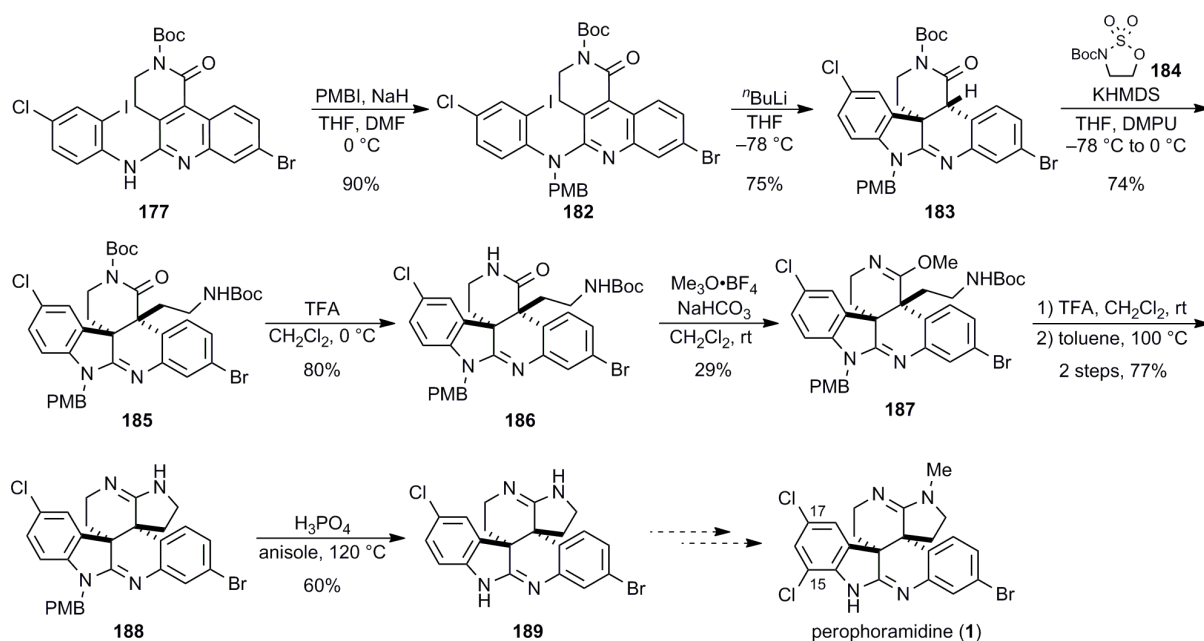
得られたジクロロ化アミノキノリン **179** から脱芳香族共役付加反応が進行しない原因については不明であるが、PMB 化反応の立体選択性の著しい変化はアニリンオルト位に位置するクロロ基の立体障害によるものと考えられた。この結果を受けて、筆者は合成戦略に修正を加え、ジクロロ化を段階的に行う計画を立案した (Scheme 56)。すなわち、**1** に含まれる 15 位塩素原子を合成終盤で求電子的塩素化反応あるいは遷移金属触媒反応によって導入できるものと期待して、17 位塩素化六環性ビスアミジン **181** を合成中間体として設定したが、この **181** の上部アルキルアミジンは求核性および配位性の観点からこれらの反応を阻害することが懸念された。そこで上部アミジンの位置選択的メチル化が Qin らによって確立されていることを踏まえ⁹、A 環の構築は先述の



Scheme 56. Revised Synthetic Strategy

第二級アミンではなく第一級アミンから行うことで、塩素化の際に予想される副反応抑制のためにアミジンを電子求引基によって保護できる余地を残した。この 17 位塩素化六環性ビスアミジン **181** はアニリンのパラ位を塩素化したアミノキノリン **182** から合成することを計画した。

これに従い、先に合成したモノ塩素化体 **177** から 17 位塩素化六環性ビスアミジンを合成した (Scheme 57)。アミノキノリン **177** への PMB 化反応は筆者の予想通り環外窒素選択的に進行し、収率 90%で鍵反応の基質であるアミノキノリン **182** を得た。塩素原子を導入したアミノキノリン **182** からの脱芳香族共役付加反応は良好に進行して収率 75%で五環性ラクタム **183** を与え、これに KHMDS とジメチルプロピレンウレア (DMPU)存在下、Dixon らによって有用性が示された環状スルファミン酸エステル **184**⁶³を作用させることによって収率 74%で Boc 保護アミノエチル化体 **185** とした。TFA によってラクタム窒素原子の Boc 基を選択的に除去して 80%の収率でラクタム **186** とし、先と同様に、ラクタム酸素原子のメチル化によって収率 29%ながらメチルイミデート **187** とした。TFA による Boc 基の除去と加熱による A 環の構築を行って六環性ビスアミジン **188** を 2 工程 77%で合成し、PMB 基を除去して収率 60%で 8 位臭素化 17 位塩素化六環性ビスアミジン **189** とした。この中間体から 15 位塩素化を経由する **1** の合成については今後の検討課題である。



Scheme 57. Synthesis of Chlorinated Hexacyclic Bisamidine

結論

本研究科において筆者は、アミナルの酸化を経由しない直接的な多環性アミジン合成による *perophoramidine* の全合成を目指して研究を行い、いずれも 2-イミノインドリンの構築を伴う独自の多環性骨格構築法を確立した。

第一の合成戦略では、分子内に不飽和カルボニル部位を有するカルボジイミドに対してヨウ化サマリウム(II)を作用させることで還元的環化反応が進行して 2-イミノインドリンが得られることを発見し、その条件最適化と基質一般性を検討した。更に、高度に官能基化された基質に対して本反応を適用することで四環性スピロイミノインドリンを合成し、続くパラジウム触媒による環化反応の条件最適化を行うことで、ラクタム α 位の異性化を伴いながら高収率で五環性アミジンが得られることを見出した。

還元的環化反応の副生成物より着想を得て取り組んだ第二の合成戦略では、分子内に 2-ヨードフェニル基を有する 2-アミノキノリンに対してリチオ化条件を適用することで 5-*exo* 型の脱芳香族共役付加反応が進行し、2-イミノインドリンを含む五環性アミジンが得られることを見出した。アミジンをもつ基質に対して本反応を適用し、続けてワンポットでアリル化を行うことで二連続第四級炭素を立体選択的に一挙構築し、*dehaloperophoramidine* の合成を達成した。更に、本反応が芳香環上の塩素原子と臭素原子を許容することを明らかにし、8 位臭素および 17 位塩素を導入した六環性ビスアミジンの合成に成功した。

参考文献

- ¹ Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124.
- ² Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 4317.
- ³ Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry* **2006**, *67*, 561.
- ⁴ Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, E.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.
- ⁵ (a) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K. Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (b) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753. (c) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **2005**, *68*, 258.
- ⁶ (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (b) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262.
- ⁷ Hendrickson, J. B.; Rees, R.; Goschke, R. *Proc. Chem. Soc.* **1962**, 383.
- ⁸ Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068.
- ⁹ Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052.
- ¹⁰ Zhang, H.; Hong, L.; Kang, H.; Wang, R. *J. Am. Chem. Soc.* **2013**, *135*, 14098.
- ¹¹ Yang, J.; Liqun, W.; Yang, J.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794.
- ¹² (a) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2000. (b) Liu, P.; Seo, J. H.; Weinreb, S. M. *J. Org. Chem.* **2010**, *75*, 2667.
- ¹³ Belmar, J.; Funk, R. L. *J. Am. Chem. Soc.* **2012**, *134*, 16941.
- ¹⁴ Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226.
- ¹⁵ Zuo, Z.; Ma, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 12008.
- ¹⁶ For synthetic studies of perophoramidine and related polycyclic amidines, (a) Artman, G. D. III; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523. (b) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y.; *Org. Lett.* **2006**, *8*, 2187. (c) Seo, J. H.; Artman, G. D. III; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8891. (d) Evans, M. A.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, *65*, 6712. (e) Voute, N.; Philp, D.; Slawin, A. M. Z.; Westwood, N. J. *Org. Biomol. Chem.* **2010**, *8*, 442. (f) Trost, B. M.; Zhang, Y. *Chem. Eur. J.* **2011**, *17*, 2916. (g) Wu, H.; Xiao, X.; Qin, Y. *Synlett* **2011**, *7*, 907.
- ¹⁷ For synthetic studies of communesins and related polycyclic amins, (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (b) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169. (c) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5762. (d) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (e) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995. (f) George, J. H.; Adlington, R. M. *Synlett* **2008**, *14*, 2093. (g) Shammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (h) Robertson, F. J.; Kenimer, B. D.; Wu, J. *Tetrahedron* **2011**, *67*, 4327. (i) Schammel, A. W.; Chiou, G.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4556.
- ¹⁸ Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854.

- ¹⁹ (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
- ²⁰ Procter, D. J.; Flowers, R. A. II; Skrydstrup, T. "Organic Synthesis using Samarium Diiodide; A Practical Guide", RSC Publishing, Cambridge, **2009**.
- ²¹ (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 7. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (d) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (e) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (f) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (g) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (h) Gopalaiiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (i) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140. (j) Szostak, M.; Procter, D. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 9238.
- ²² (a) Fukuzawa, S.-i.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (b) Fukuzawa, S.-i.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1669.
- ²³ Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.
- ²⁴ Enholm, E. J.; Trivellas, A. *Tetrahedron* **1989**, *30*, 1063.
- ²⁵ (a) Fukuzawa, S.-i.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (b) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (c) Molander, G. A.; Kenny, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (d) Kito, M.; Sakai, T.; Yamada, K. Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (e) Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305. (f) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (g) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (h) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1997**, *38*, 7199. (i) Merlic, C. A.; Walsh, J.C. *Tetrahedron Lett.* **1998**, *39*, 2083. (j) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (k) Matsuda, F.; Kawatsura, M.; Hosaka, K.-i.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252. (l) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371. (m) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (n) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859. (o) Sono, M.; Nakashiba, Y.; Nakashima, K. Tori, M. *J. Org. Chem.* **2000**, *65*, 3099. (p) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345. (q) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653. (r) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811. (s) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190. (t) Helm, M. D.; Sucunza, D.; Da Silva, M.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224. (u) Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron* **2009**, *65*, 10816.
- ²⁶ (a) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (b) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501. (c) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229. (d) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773. (e) Merlic, C. A.; Walsh, J. C. *J. Org. Chem.* **2001**, *66*, 2265. (f) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (g) Wang, W.; Zhong, Y.; Lin, G. *Tetrahedron Lett.* **2003**, *44*, 4613. (h) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402. (i) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476. (j) Huang, L.-L.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2005**, *70*, 529. (k) Zhang, Y.; Wang, Y.; Dai, W.-M. *J. Org. Chem.* **2006**, *71*, 2445.

- ²⁷ (a) Enholm, E. J.; Satıcı, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841. (b) Tadano, K.-i.; Isshiki, Y.; Minami, M.; Ogawa, S. *Tetrahedron Lett.* **1992**, *33*, 7899. (c) Tadano, K.-i.; Isshiki, Y.; Minami, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 6266. (d) Arseniyadis, S.; Yashunsky, D. V.; Muñoz Dorado, M.; Brondi Alves, R.; Toromanoff, E.; Toupet, L.; Ptier, P. *Tetrahedron Lett.* **1993**, *34*, 4927. (e) Schwaebe, M.; Little, R. D. *J. Org. Chem.* **1996**, *61*, 3240. (f) Alcón, M.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron; Asymmetry* **1997**, *8*, 2967. (g) Banwell, M.; McLeod, M. *Chem. Commun.* **1998**, 1851. (h) Matsuo, G.; Mastukura, H.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 7673. (i) Carroll, G. L.; Little, R. D. *Org. Lett.* **2000**, *2*, 2873. (j) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52. (k) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1090. (l) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001. (m) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853. (n) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033. (o) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 3943. (p) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. *New J. Chem.* **2003**, *27*, 50. (q) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893. (r) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003**, *1*, 328. (s) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374. (t) Kerrigan, N. J.; Upadhyay, T.; Procter, D. J. *Tetrahedron Lett.* **2004**, *45*, 9087. (u) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648. (v) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989. (w) Peltier, H. M.; McMahon, J. P.; Patterton, A. W.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 16018. (x) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 3942. (y) Ebine, M.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2275. (z) Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5631. (aa) Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9315. (bb) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
- ²⁸ Kim, Y. H.; Park, H. S.; Kwon, D. W. *Synth. Comm.* **1998**, *28*, 4517.
- ²⁹ McDonald, C. E.; Galka, A. M. Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D. *Tetrahedron Lett.* **2001**, *42*, 163.
- ³⁰ (a) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 2265. (b) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallée, Y. *Synlett* **2003**, *10*, 1527. (c) Desvergnès, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (d) Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2007**, *72*, 485. (e) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042.
- ³¹ (a) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229. (b) Johannesen, S. A.; Albu, S.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun.* **2004**, 1962.
- ³² (a) Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, *125*, 4030. (b) Lindsay, K.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 4766.
- ³³ (a) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. W.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1270. (b) Reisman, S. E.; Ready, J. M.; Weiss, M. W.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087.
- ³⁴ Deng, M.; Yao, Y.; Zhang, Y.; Shen, Q. *Chem. Commun.* **2004**, 2742.

- ³⁵ (a) Chang, D.; Feiten, H.-J.; Witholt, B.; Li, Z. *Tetrahedron; Asymmetry* **2002**, *13*, 2141. (b) Žerovnik, D.; Grošelj, U.; Kralj, D.; Malavašič, Č.; Bezenšek, J.; Dahmann, G.; Stare, K.; Meden, A.; Stanovnik, B.; Svete, J. *Synthesis* **2010**, *19*, 3363.
- ³⁶ (a) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607. (b) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
- ³⁷ (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- ³⁸ Ikegashira, K.; Oka, T.; Hirashima, S.; Noji, S.; Yamanaka, H.; Hara, Y.; Adachi, T.; Tsuruha, J.-I.; Doi, S.; Hase, Y.; Noguchi, T.; Ando, I.; Ogura, N.; Ikeda, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 6950.
- ³⁹ Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.
- ⁴⁰ (a) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A. II, *Tetrahedron Lett.* **1997**, *38*, 8157. (b) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A. II, *J. Am. Chem. Soc.* **2000**, *122*, 7718. (c) Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633.
- ⁴¹ Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, *40*, 7497.
- ⁴² Guazzelli, G.; Duffy, L. A.; Procter, D. *J. Org. Lett.* **2008**, *10*, 4291.
- ⁴³ (a) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (b) Bachi, M. D.; Derenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886. (c) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (d) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2683.
- ⁴⁴ (a) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. (b) Baechler, S. A.; Fehr, M.; Habermeyer, M.; Hofmann, A.; Merz, K.-H.; Fiebig, H.-H.; Marko, D.; Eisenbrand, G. *Bioorg. Med. Chem.* **2013**, *21*, 814.
- ⁴⁵ (a) Brain, C.; Brunton, T. *Tetrahedron Lett.* **2002**, *43*, 1893. (b) McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 3800.
- ⁴⁶ (a) Zepf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413. (e) Huser, M.; Youinou, M.-T.; Osborn, J. A. *Angew. Chem. Int. Ed.* **1989**, *28*, 1386. (f) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.
- ⁴⁷ (a) Saito, T.; Ohmori, H.; Furuno, E.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 22. (b) Molina, P.; Alajarín, M.; Vidal, A.; Sánchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929.
- ⁴⁸ (a) Mander, L. N. *Synlett* **1991**, 134. (b) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (c) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137. (d) López-Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andújar-Sánchez, C. M.; Ruiz-Gómez, G. *Chem. Rev.* **2007**, *107*, 1580. (e) Roche, S. P.; Porco, J. A. Jr. *Angew. Chem. Int. Ed.* **2011**, *50*, 4068. (f) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12662. (g) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642.
- ⁴⁹ (a) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865. (b) Meyers, A. I.; Barner, B. A. *J.*

- Org. Chem.* **1986**, *51*, 120. (c) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5279. (d) Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107. (e) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
- ⁵⁰ (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (b) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1739. (c) Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276. (d) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681. (e) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955.
- ⁵¹ (a) Ahmed, A.; Clayden, J.; Rowly, M. *Chem. Commun.* **1998**, 297. (b) Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, *4*, 787. (c) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411.
- ⁵² Andújar Sánchez, C. M.; José Iglesias, M.; López Ortiz, F. *Tetrahedron Lett.* **2002**, *43*, 2565.
- ⁵³ Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. *J. Org. Chem.* **2007**, *72*, 3484.
- ⁵⁴ Banwell, M. G.; Jones, M. T.; Loong, D. T. J.; Lupton, D. W.; Pinkerton, D. M.; Ray, J. K.; Willis, A. C. *Tetrahedron* **2010**, *66*, 9252.
- ⁵⁵ Ali, A. R.; Ghosh, H.; Patel, B. K. *Tetrahedron Lett.* **2010**, *51*, 1019.
- ⁵⁶ (a) Lecher, H. Z.; Greenwood, R. A.; Whitehouse, K. C.; Chao, T. H. *J. Am. Chem. Soc.* **1956**, *78*, 5018. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (c) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, *13*, 1929. and reference therein.
- ⁵⁷ (a) Snead, D. R.; Inagaki, S.; Abboud, K. A.; Hong, S. *Organometallics* **2010**, *29*, 1729. (b) Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3190.
- ⁵⁸ (a) Bolm, C.; Rudolph, C. *J. Am. Chem. Soc.* **2002**, *124*, 12850. (b) Son, S. U.; Kim, S. B.; Reingold, J. A.; Carpenter, G. B.; Sweigart, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 12238.
- ⁵⁹ Kienzle, F.; Kaiser, A.; Chodnekar, M. S. *Eur. J. Med. Chem.* **1982**, *17*, 547.
- ⁶⁰ (a) Amgen Inc.; Chen, G.; Cushing, T. D.; Fisher, B.; He, X.; Li, K.; Li, Z.; McGee, L. R.; Pattarpong, V.; Faulder, P.; Seganish, J. L.; Shin, Y. WO Patent 2009158011 (A1), **2009**. (b) IRM LLC; Mi, Y.; Albaugh, P.; Fan, Y.; Choi, H.-S.; Liu, Z.; Huang, S. WO Patent 2008073480 (A1), **2008**.
- ⁶¹ Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
- ⁶² Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.
- ⁶³ Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 568.

実験項

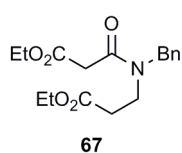
General. Unless otherwise noted, all reactions were performed under an argon atmosphere. Analytical thin-layer chromatography was performed with Merck TLC Silica gel 60 F₂₅₄ or Fuji Silysia Chromatorex NH. Preparative thin-layer chromatography was performed with Merck PLC Silica gel 60 F₂₅₄ or Fuji Silysia Chromatorex NH. Silica gel column chromatography was performed with Kanto Silica gel 60 N (spherical, neutral, 40-100 μm), Fuji Silysia Chromatorex BW-300, or Fuji Silysia Chromatorex NH silica gel. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00, in the case of CDCl_3), $\text{DMSO}-d_6$ (δ 2.53) or $\text{CF}_3\text{CO}_2\text{D}$ (δ 11.50). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 125 MHz. Chemical shifts are reported relative to CDCl_3 (δ 77.0), $\text{DMSO}-d_6$ (δ 39.5) or $\text{CF}_3\text{CO}_2\text{D}$ (δ 164.2). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Infrared spectra were recorded on FT/IR-4100 (JASCO). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on JEOL JMS-700 (FAB+). X-ray crystallographic data were recorded on RIGAKU R-AXIS RAPID.

General procedure for synthesis of carbodiimides from corresponding ureas. To a solutions of urea (170 μmol), PPh_3 (66.8 mg, 255 μmol), and Et_3N (52.0 μL , 374 μmol) in 2 mL of CH_2Cl_2 , was added CBr_4 (67.7 mg, 204 μmol) at 0 $^\circ\text{C}$. These reaction mixtures were stirred for 2 hours and warmed to ambient temperature. Then additional PPh_3 (134 mg, 510 μmol) was added. After 3-15 hours, the reaction mixtures were directly evaporated. These resultant residues were purified by silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 8/2$ to $7/3$) to give carbodiimides.

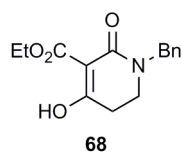
General procedure for SmI_2 -mediated reductive cyclization (condition A). To solutions of SmI_2 (0.1 M prepared from 1,2-diiodoethane and metal Sm in THF, 2.4 mL, 240 μmol) at ambient temperature, were added solutions of carbodiimide (100 μmol) and $^t\text{BuOH}$ (21.0 μL , 220 μmol) in 2 mL of THF in a dropwise manner. After 15 minutes, saturated aqueous NH_4Cl solutions were added to these reaction mixtures and the organic solvents were removed by evaporation. These aqueous solutions were extracted with AcOEt. The organic layers were extracted with 1 M aqueous HCl solutions and the resultant aqueous layers were neutralized with solid NaHCO_3 . These aqueous layers were extracted with AcOEt and the organic layers were dried over Na_2SO_4 . These crude solutions were concentrated under reduced pressure and dried in vacuo. To solutions of Boc_2O (32.7 mg, 150 μmol) in 1 mL of CH_2Cl_2 , were added solutions of the crude material in 2 mL of CH_2Cl_2 at ambient temperature. Then DMAP (12.2 mg, 100 μmol) were added and reaction mixtures were stirred for 10-20 hours. The mixtures were evaporated and directly subjected to silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 9/1$ to $7/3$) to give *N*-Boc protected iminoindolines.

General procedure for SmI_2 -mediated reductive cyclization (condition B). Solutions of carbodiimide

(100 μmol) and $t\text{BuOH}$ (95.6 μL , 1.00 mmol) in 2 mL of THF were degassed by freeze pump thaw cycles chilled with liquid nitrogen. To these solutions at ambient temperature, were added solutions of SmI_2 (0.1 M in THF, 2.1 mL, 210 μmol) in a dropwise manner. After 15 minutes, saturated aqueous NH_4Cl solutions were added to the reaction mixtures and the organic solvents were removed by evaporation. The resultant mixtures were extracted with AcOEt and the organic layers were washed with saturated aqueous NH_4Cl solutions and dried over Na_2SO_4 . The crude solutions were concentrated under reduced pressure and dried in vacuo. To solutions of Boc_2O (32.7 mg, 0.150 mmol) in 1 mL of CH_2Cl_2 , were added the solutions of these crude materials in 2 mL of CH_2Cl_2 at ambient temperature. Then DMAP (12.2 mg, 100 μmol) was added and the reaction mixtures were stirred for 5-20 hours. The mixtures were evaporated and directly subjected to silica gel column chromatography ($n\text{hexane}/\text{AcOEt} = 8/2$ to $6/4$) to give *N*-Boc protected iminoindolines.

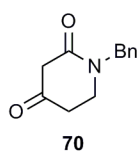


Ethyl 3-(Benzyl(3-ethoxy-3-oxopropyl)amino)-3-oxopropanoate (67) To a solution of ethyl 3-(*N*-benzylamino)propionate (414 mg, 2.00 mmol) and $t\text{Pr}_2\text{NEt}$ (342 μL , 2.00 mmol) in 4 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added ethyl malonyl chloride (303 μL , 2.40 mmol). The reaction mixture was warmed to ambient temperature and stirred for 10 minutes. H_2O was added at 0 $^\circ\text{C}$ and the separated aqueous layer was extracted with CHCl_3 . The combined organic layers were washed with a saturated aqueous NaHCO_3 solution and with brine. The crude material was dried over Na_2SO_4 , concentrated under reduced pressure and purified by silica gel column chromatography (AcOEt) to give titled compound (598 mg, 93%) as a viscous colorless oil; ^1H NMR (CDCl_3 , δ) 7.32-7.27 (m, 5H), 4.65 (s, 2H), 4.61* (s, 2H), 4.25-4.08 (m, 4H), 3.65 (t, 2H, $J = 6.9$ Hz), 3.56* (t, 2H, $J = 6.9$ Hz), 3.44 (s, 2H), 2.65, (t, 2H, $J = 6.9$ Hz), 2.54* (t, 2H, $J = 6.9$ Hz), 1.31-1.22 (m, 6H); ^{13}C NMR (CDCl_3 , δ) 171.9, 170.9*, 167.4, 167.6*, 166.7, 166.5*, 136.7*, 136.2, 129.0, 128.6, 127.8, 127.8, 127.4, 126.3, 61.5*, 61.4, 61.0*, 60.5, 52.7, 47.9*, 43.1*, 43.0, 41.4, 41.1*, 33.1*, 32.5, 14.1*, 14.1, 14.0; IR (ATR) 1736, 1654 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.68; H, 7.29; N, 4.39. HRMS (MH^+) calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5$: 322.1654. Found: 322.1654 (* peaks of minor conformer).

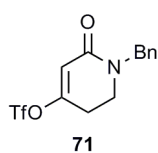


Ethyl 1-Benzyl-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (68) To 80 mL of EtOH, was added NaH (60%wt, 708 mg, 17.7 mmol) at 0 $^\circ\text{C}$. Ethyl ester **67** (5.18 g, 16.1 mmol) in 20 mL of EtOH was added dropwise over 10 minutes at the same temperature. The reaction mixture was warmed to ambient temperature and stirred for 12 hours. A 2.0 M aqueous HCl solution was added and the resultant solution was evaporated. The residue was dissolved in H_2O and extracted with CHCl_3 three times (pH of the aqueous layer < 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ($n\text{hexane}/\text{AcOEt} = 6/4$ to $4/6$) to give the titled compound (4.03 g, 91%) as a viscous colorless oil; ^1H NMR (CDCl_3 , δ) 7.34-7.27 (m, 5H), 4.64 (s, 2H), 4.41 (q, 2H, $J = 7.2$ Hz), 3.32 (t, 2H, $J = 6.9$ Hz), 2.54 (t, 2H, $J = 6.9$ Hz), 1.42 (t, 2H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , δ) 128.9, 172.0, 137.7, 128.6, 128.0, 127.4, 98.2, 61.8, 49.4, 41.5, 29.6, 14.2; IR (CHCl_3) 1729, 1658 cm^{-1} ;

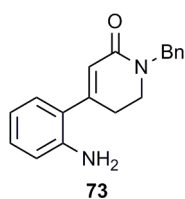
HRMS (MH⁺) calcd for C₁₅H₁₈NO₄: 276.1236. Found: 276.1244.



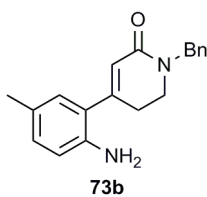
1-Benzylpiperidine-2,4-dione (70) A solution of ethyl carboxylate **69** (3.78 g, 13.7 mmol) and 0.1 mL of H₂O in 100 mL of MeCN was heated to reflux for 3.5 hours. The reaction mixture was evaporated and purified by silica gel column chromatography (CHCl₃/MeOH = 98/2 to 95/5) to give the titled compound (2.73 g, 98%) as a colorless solid; mp 59-60 °C; ¹H NMR (CDCl₃, δ) 7.34-7.26 (m, 5H), 4.69 (s, 2H), 3.49 (t, 2H, *J* = 6.0 Hz), 3.43 (s, 2H), 2.54 (t, 2H, *J* = 6.0 Hz); ¹³C NMR (CDCl₃, δ) 203.4, 166.3, 136.2, 128.8, 128.0, 127.9, 50.0, 48.9, 42.3, 38.6; IR (ATR) 1715, 1651 cm⁻¹; MS (FAB⁺) *m/z* = 204 (MH⁺); Anal. Calcd for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.78; H, 6.48; N, 6.85.



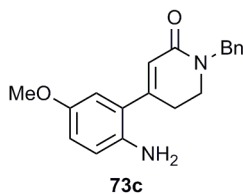
1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl Trifluoromethanesulfonate (71) To a solution of lactam **70** (6.09 g, 30.0 mmol) and Et₃N (8.35 mL, 60.0 mmol) in 100 mL of CH₂Cl₂ at 0 °C, was added Tf₂NPh (12.9 g, 36.0 mmol). After an hour, the reaction mixture was warmed to ambient temperature and stirred for 2 hours. A 0.1 M aqueous HCl solution was added to the mixture at 0 °C and the separated aqueous layer was extracted with CHCl₃. The combined organic layers were washed with 0.1 M aqueous HCl solution, with brine, with a saturated aqueous NaHCO₃ solution and with brine. The resultant solution was dried over Na₂SO₄ and concentrated under reduced pressure. This crude material was purified by silica gel column chromatography (hexane/AcOEt = 9/1 to 8/2) to give the titled compound (9.81 g, 97%) as a colorless oil; ¹H NMR (CDCl₃, δ) 7.35-7.28 (m, 5H), 6.06 (s, 1H), 4.62 (s, 2H), 3.44 (t, 2H, *J* = 7.2 Hz), 2.69 (t, 2H, *J* = 7.2 Hz); ¹³C NMR (CDCl₃, δ) 162.7, 157.5, 136.3, 128.7, 127.9, 127.9, 127.7, 118.3 (q, *J* = 320.7 Hz), 114.2, 49.3, 43.3, 27.1; IR (ATR) 1680, 1366, 1219 cm⁻¹; MS (FAB⁺) *m/z* = 336 (MH⁺); Anal. Calcd for C₁₃H₁₂F₃NO₄S: C, 46.57; H, 3.61; N, 4.18. Found: C, 46.52; H, 3.61; N, 4.28.



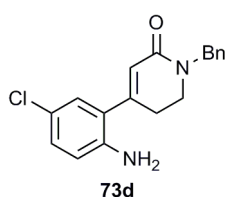
4-(2-Aminophenyl)-1-benzyl-5,6-dihydropyridin-2(1H)-one (73) A solution of boronic acid pinacol ester **72** (876 mg, 4.00 mmol), alkenyl triflate **71** (1.65 g, 4.84 mmol) and PdCl₂(PPh₃)₂ (140 mg, 200 μmol) in 50 mL of THF and 32 mL of a 2.0 M aqueous Na₂CO₃ solution was heated to reflux for 12 hours. After the reaction mixture was cooled to ambient temperature, the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/AcOEt = 5/5 to 3/7) to give the titled compound (1.05 g, 95%) as a colorless solid; mp 110-112 °C; ¹H NMR (CDCl₃, δ) 7.37-7.27 (m, 5H), 7.13 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.05 (d, 1H, *J* = 7.5 Hz), 6.77 (dd, 1H, *J* = 7.5, 7.5 Hz), 6.72 (d, 1H, *J* = 7.5 Hz), 6.23 (s, 1H), 4.69 (s, 2H), 3.93 (br, 2H), 3.45 (t, 2H, *J* = 6.7 Hz), 2.67 (t, 2H, *J* = 6.7 Hz); ¹³C NMR (CDCl₃, δ) 165.0, 150.0, 143.1, 137.4, 129.6, 128.7, 128.1, 128.0, 127.5, 124.5, 122.6, 118.6, 116.3, 49.7, 44.9, 28.8; IR (ATR) 3415, 3333, 1630 cm⁻¹; HRMS (MH⁺) calcd for C₁₈H₁₉N₂O: 279.1497. Found: 279.1499.



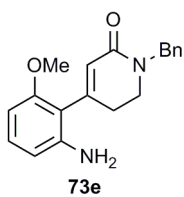
4-(2-Amino-5-methylphenyl)-1-benzyl-5,6-dihydropyridin-2(1H)-one (73b) To a solution of *N*-Boc aniline **99b** (228 mg, 582 μmol) in 4.5 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 0.5 mL of TFA. The reaction mixture was warmed to ambient temperature and stirred for 16 hours. To the mixture was added a saturated aqueous NaHCO_3 solution and the aqueous layer was extracted with CHCl_3 . The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 6/4 to 5/5) to give the titled compound (141 mg, 83%) as a yellow solid; mp 100-101 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.35-7.24 (m, 5H), 6.91 (dd, 1H, $J = 8.2, 1.9$ Hz), 6.84 (s, 1H), 6.61 (d, 1H, $J = 8.2$ Hz), 6.19 (s, 1H), 4.66 (s, 2H), 3.79 (br s, 2H), 3.42 (t, 2H, $J = 7.0$ Hz), 2.64 (t, 2H, $J = 7.0$ Hz), 2.21 (s, 3H); ^{13}C NMR (CDCl_3 , δ) 164.9, 150.2, 140.8, 137.2, 130.1, 128.5, 128.2, 127.9, 127.4, 122.1, 116.3, 49.5, 44.7, 28.5, 20.2; IR (ATR) 3404, 1635 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}$: 293.1654. Found: 293.1652.



4-(2-Amino-5-methoxyphenyl)-1-benzyl-5,6-dihydropyridin-2(1H)-one (73c) To a solution of *N*-Boc aniline **99c** (286 mg, 700 μmol) in 3.8 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 0.6 mL of TFA. The reaction mixture was warmed to ambient temperature and stirred for an hour. To the mixture was added a saturated aqueous NaHCO_3 solution and the aqueous layer was extracted with CHCl_3 . The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 6/4 to 5/5) to give the titled compound (177 mg, 82%) as a yellow solid; mp 94-95 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.33-7.24 (m, 5H), 6.70 (dd, 1H, $J = 8.7, 1.9$ Hz), 6.63 (d, 1H, $J = 8.7$ Hz), 6.60 (d, 1H, $J = 1.9$ Hz), 6.19 (s, 1H), 4.64 (s, 2H), 3.68 (d, 3H, $J = 0.9$ Hz), 3.58 (br, 2H), 3.40 (t, 2H, $J = 7.0$ Hz), 2.63 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , δ) 164.6, 152.0, 150.0, 137.01, 136.98, 128.3, 127.7, 127.1, 125.1, 122.3, 117.4, 115.4, 112.8, 55.4, 49.3, 44.5, 28.1; IR (ATR) 3337, 1654 cm^{-1} ; HRMS (M^+) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$: 308.1525. Found: 308.1522.



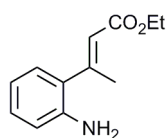
4-(2-Amino-5-chlorophenyl)-1-benzyl-5,6-dihydropyridin-2(1H)-one (73d) To a solution of *N*-Boc aniline **99d** (278 mg, 673 μmol) in 2.7 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 0.3 mL of TFA. The reaction mixture was warmed to ambient temperature and stirred for 17 hours. To the mixture was added a saturated aqueous NaHCO_3 solution and the aqueous layer was extracted with CHCl_3 . The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 6/4 to 4/6) to give the titled compound (184 mg, 87%) as a yellow oil; ^1H NMR (CDCl_3 , δ) 7.37-7.28 (m, 5H), 7.07 (dd, 1H, $J = 8.6, 2.6$ Hz), 7.02 (d, 1H, $J = 2.6$ Hz), 6.65 (d, 1H, $J = 8.6$ Hz), 6.22 (t, 1H, $J = 1.4$ Hz), 4.68 (s, 2H), 3.90 (br, 2H), 3.45 (t, 2H, $J = 7.0$ Hz), 2.63 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , δ) 164.6, 148.6, 141.8, 137.2, 129.3, 128.7, 128.1, 127.6, 127.5, 125.5, 123.3, 123.1, 117.4, 49.7, 44.7, 28.6; IR (ATR) 3403, 1632 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{18}\text{H}_{18}^{35}\text{ClN}_2\text{O}$: 312.1108. Found: 312.1109.



73e

4-(2-Amino-6-methoxyphenyl)-1-benzyl-5,6-dihydropyridin-2(1H)-one (73e) To a solution of *N*-Boc aniline **99e** (143 mg, 350 μ mol) in 3 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 0.3 mL of TFA. The reaction mixture was warmed to ambient temperature and stirred for 13 hour. To the mixture was added a saturated aqueous NaHCO_3 solution and the aqueous layer was extracted with CHCl_3 . The combined organic layers were dried

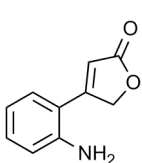
over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 6/4 to 4/6) to give the titled compound (92.3 mg, 85%) as a yellow oil; ^1H NMR (CDCl_3 , δ) 7.35-7.28 (m, 5H), 7.05 (dd, 1H, J = 8.0, 8.0 Hz), 6.36 (d, 1H, J = 8.0 Hz), 6.30 (d, 1H, J = 8.0 Hz), 6.05 (s, 1H), 4.69 (s, 2H), 3.88 (br s, 2H), 3.74 (s, 3H), 3.44 (t, 2H, J = 6.9 Hz), 2.56 (br s, 2H); ^{13}C NMR (CDCl_3 , δ) 164.8, 157.3, 148.7, 143.9, 137.4, 129.5, 128.6, 128.2, 127.4, 124.2, 113.6, 108.6, 100.6, 55.5, 49.7, 45.1, 28.7; IR (ATR) 3446, 1652 cm^{-1} ; HRMS (M^+) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$: 308.1525. Found: 308.1522.



73k

(E)-Ethyl 3-(2-Aminophenyl)but-2-enoate (73k) A solution of alkenyl triflate ($E/Z > 95/5$, 157 mg, 599 μ mol), boronic acid pinacol ester **72** (171 mg, 779 μ mol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (20.1 mg, 28.6 μ mol) in 5 mL of THF and 5 mL of a 1.9 M aqueous Na_2CO_3 solution was heated to reflux for 2 hours. The reaction mixture was cooled to ambient

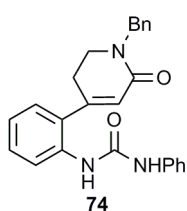
temperature. The aqueous layer was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 9/1 to 8/2) to give the titled compound (*E* only, 91.5 mg, 74%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.11 (ddd, 1H, J = 7.5, 7.5, 1.4 Hz), 7.01 (dd, 1H, J = 7.5, 1.4 Hz), 6.75 (ddd, 1H, J = 7.5, 7.5, 1.4 Hz), 6.70 (d, 1H, J = 7.5 Hz), 5.97 (t, 1H, J = 1.4 Hz), 4.21 (q, 2H, J = 7.2 Hz), 3.76 (br, 2H), 2.49 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz); ^{13}C NMR (CDCl_3 , δ) 166.5, 155.7, 142.4, 129.2, 128.8, 127.9, 119.6, 118.2, 115.8, 59.8, 24.8, 19.8, 14.2; IR (ATR) 3374, 1709 cm^{-1} ; HRMS (M^+) calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: 205.1103. Found: 205.1102.



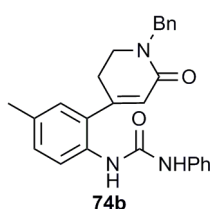
73l

4-(2-Aminophenyl)furan-2(5H)-one (73l) A solution of boronic acid pinacol ester **72** (439 mg, 2.00 mmol), alkenyl triflate (554 mg, 2.40 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (70.2 mg, 100 μ mol) in 10 mL of THF and 10 mL of a 2.0 M aqueous Na_2CO_3 solution was heated to 80 $^\circ\text{C}$ for 22 hours. The reaction mixture was cooled to ambient temperature. The aqueous layer was extracted with AcOEt twice. The combined organic layers were washed with

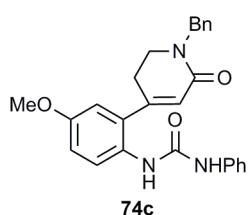
brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 8/2 to 6/4) to give the titled compound (115 mg, 33%) as a yellow crystal; mp 40-41 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.28-7.26 (m, 1H), 7.12 (d, 1H, J = 7.2 Hz), 6.85-6.82 (m, 2H), 6.39 (t, 1H, J = 1.6 Hz), 5.21 (d, 2H, J = 1.6 Hz), 4.13 (br, 2H); ^{13}C NMR (CDCl_3 , δ) 161.9, 146.0, 132.3, 127.4, 119.0, 117.6, 115.4, 114.0, 72.2; IR (ATR) 3345, 1652 cm^{-1} ; MS (FAB $^+$) m/z = 176 (MH^+); Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_2$: C, 68.58; H, 5.18; N, 8.00. Found: C, 68.34; H, 5.09; N, 8.00.



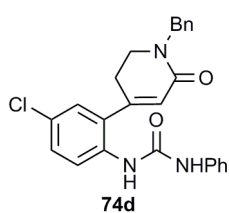
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-phenylurea (74). To a solution of aniline **73** (278 mg, 1.00 mmol) in 3 mL of CH₂Cl₂, was added PhNCO (110 μL, 1.05 mmol) at ambient temperature. After 7.5 hours additional PhNCO (20.0 μL, 150 μmol) was added. After 3 hours the reaction mixture was directly subjected to silica gel column chromatography (ⁿhexane/AcOEt = 8/2 to 6/4) to give the titled compound (337 mg, 98%) as a colorless solid; mp 184-186 °C; ¹H NMR (CDCl₃, δ) 8.41 (s, 1H), 8.26 (s, 1H), 8.00 (d, 1H, *J* = 8.6 Hz), 7.34-7.31 (m, 8H), 7.18 (dd, 2H, *J* = 7.7, 7.7 Hz), 7.07-7.01 (m, 2H), 6.96 (dd, 1H, *J* = 7.4, 7.4 Hz), 5.88 (s, 1H), 4.61 (s, 2H), 3.52 (t, 2H, *J* = 6.9 Hz), 2.75 (t, 2H, *J* = 6.9 Hz); ¹³C NMR (CDCl₃, δ) 165.4, 153.8, 153.1, 139.4, 136.0, 135.4, 130.8, 129.7, 129.0, 128.9, 127.9, 127.7, 127.6, 123.3, 123.1, 122.6, 122.4, 118.7, 50.3, 45.8, 28.4; IR (ATR) 3269, 1651, 1634 cm⁻¹; MS (FAB⁺) *m/z* = 398 (MH⁺); Anal. Calcd for C₂₅H₂₃N₃O₂: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.54; H, 5.87; N, 10.52.



1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-methylphenyl)-3-phenylurea (74b) To a solution of aniline **73b** (129 mg, 442 μmol) in 2.5 mL of CH₂Cl₂, were added PhNCO (52.6 μL, 486 μmol) and DMAP (2.3 mg, 18.9 μmol) at ambient temperature. The mixture was heated to reflux for 17 hours. Then the reaction mixture was directly subjected to silica gel column chromatography (ⁿhexane/AcOEt = 8/2 to 6/4) to give the titled compound (163 mg, 90%) as a colorless solid; mp 192-193 °C; ¹H NMR (CDCl₃, δ) 8.20 (s, 1H), 8.03 (s, 1H), 7.83 (d, 1H, *J* = 8.0 Hz), 7.38-7.28 (m, 7H), 7.19 (dd, 2H, *J* = 8.0, 8.0 Hz), 7.14 (dd, 1H, *J* = 8.0, 1.7 Hz), 6.96 (dd, 1H, *J* = 7.4, 7.4 Hz), 6.90 (d, 1H, *J* = 1.7 Hz), 5.88 (s, 1H), 4.61 (s, 2H), 3.49 (t, 2H, *J* = 6.9 Hz), 2.72 (t, 2H, *J* = 6.9 Hz), 2.28 (s, 3H); ¹³C NMR (CDCl₃, δ) 165.3, 153.8, 153.3, 139.4, 136.1, 133.1, 132.6, 131.1, 130.1, 128.9, 128.8, 128.2, 127.8, 127.6, 123.5, 122.2, 122.1, 118.5, 50.1, 45.7, 28.3, 20.6; IR (ATR) 3345, 1710, 1655 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₂₆N₃O₂: 412.2025. Found: 412.2028.

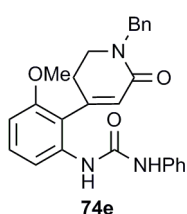


1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-methoxyphenyl)-3-phenylurea (74c) To a solution of aniline **73c** (159 mg, 516 μmol) in 2.5 mL of CH₂Cl₂, were added PhNCO (61.4 μL, 568 μmol) and DMAP (2.6 mg, 21.3 μmol) at ambient temperature. The mixture was heated to reflux for 14 hours. The reaction mixture was directly subjected to silica gel column chromatography (ⁿhexane/AcOEt = 6/4 to 4/6) to give the titled compound (151 mg, 67%) as a colorless solid; mp 97-98 °C; ¹H NMR (CDCl₃, δ) 8.29 (s, 1H), 8.11 (s, 1H), 7.61 (d, 1H, *J* = 8.9 Hz), 7.29-7.25 (m, 7H), 7.13-7.12 (m, 2H), 6.93-6.91 (m, 1H), 6.81-6.79 (m, 1H), 6.62 (d, 1H, *J* = 2.6 Hz), 5.84 (s, 1H), 4.56 (s, 2H), 3.72 (s, 3H), 3.44 (t, 2H, *J* = 6.9 Hz), 2.68 (t, 2H, *J* = 6.9 Hz); ¹³C NMR (CDCl₃, δ) 165.1, 156.1, 153.7, 153.1, 139.3, 136.1, 133.6, 128.8, 138.7, 127.8, 127.7, 127.5, 126.3, 122.3, 122.2, 118.5, 114.7, 112.9, 55.4, 50.0, 45.6, 28.2; IR (ATR) 3304, 1649 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₂₆N₃O₃: 428.1974. Found: 428.1979.



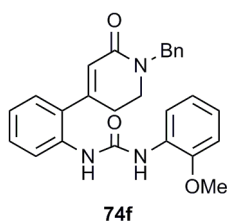
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-chlorophenyl)-3-phenylurea (74d)

To a solution of aniline **73d** (145 mg, 463 μmol) in 2.5 mL of CH_2Cl_2 , were added PhNCO (55.1 μL , 509 μmol) and DMAP (2.6 mg, 21.3 μmol) at ambient temperature. The mixture was heated to reflux for 23 hours. The reaction mixture was directly subjected to silica gel column chromatography (hexane/AcOEt = 6/4 to 4/6) to give the titled compound (171 mg, 86%) as a colorless solid; mp 149-150 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 8.41 (s, 1H), 8.35 (s, 1H), 7.96 (d, 1H, $J = 8.9$ Hz), 7.36-7.23 (m, 8H), 7.17 (dd, 2H, $J = 7.9$, 7.9 Hz), 7.06 (d, 1H, $J = 2.6$ Hz), 6.96 (dd, 1H, $J = 7.4$, 7.4 Hz), 5.86 (s, 1H), 4.59 (s, 2H), 3.51 (t, 2H, $J = 6.9$ Hz), 2.71 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , δ) 165.0, 152.8, 152.2, 139.0, 135.7, 134.1, 131.8, 129.4, 129.0, 128.8, 128.2, 127.9, 127.5, 127.4, 124.1, 123.1, 122.5, 118.6, 50.3, 45.7, 28.0; IR (ATR) 3362, 1644 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{23}^{35}\text{ClN}_3\text{O}_2$: 432.1479. Found: 432.1481.



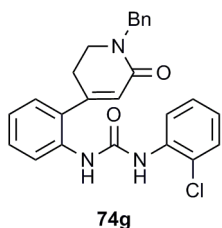
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-3-methoxyphenyl)-3-phenylurea (74e)

To a solution of aniline **73e** (112 mg, 360 μmol) in 3 mL of CH_2Cl_2 , were added PhNCO (42.8 μL , 396 μmol) and DMAP (6.7 mg, 54.8 μmol) at ambient temperature. The mixture was stirred for 18 hours. Et_2O was added to the mixture and filtration gave the titled compound (132 mg, 86%) as a colorless solid; mp 181-182 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 8.35 (s, 1H), 7.80-7.78 (m, 2H), 7.37-7.24 (m, 9H), 7.21 (dd, 2H, $J = 8.0$, 8.0 Hz), 6.98 (dd, 1H, $J = 7.4$, 7.4 Hz), 6.60 (d, 1H, $J = 8.0$ Hz), 5.93 (s, 1H), 5.09 (brs, 1H), 4.29 (brs, 1H), 3.73 (s, 3H), 3.53 (t, 2H, $J = 7.0$ Hz), 2.60 (brs, 2H); ^{13}C NMR (CDCl_3 , δ) 165.5, 155.9, 153.2, 149.3, 139.4, 136.4, 129.4, 128.9, 128.8, 127.8, 127.7, 124.6, 122.3, 119.0, 118.7, 114.5, 105.1, 55.6, 50.0, 45.5, 28.5; IR (ATR) 3356, 1650 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_3$: 428.1974. Found: 428.1968.



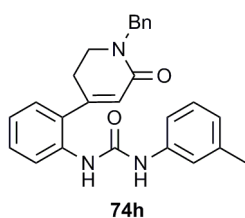
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-(2-methoxyphenyl)urea (74f)

A solution of aniline **73** (139 mg, 500 μmol), 2-methoxyphenyl isocyanate (73.1 μL , 550 μmol) and DMAP (6.1 mg, 50.0 μmol) in 3 mL of CH_2Cl_2 was heated at 60 $^\circ\text{C}$ for 23 hours in a sealed tube. The reaction mixture was directly evaporated and subjected to silica gel column chromatography ($\text{CHCl}_3/\text{AcOEt} = 1/0$ to 9/1) to give the titled compound (159 mg, 74%) as a colorless solid; mp 177-178 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 8.61 (s, 1H), 8.23-8.22 (m, 2H), 7.86 (d, 1H, $J = 8.3$ Hz), 7.30-7.26 (m, 6H), 7.09-7.03 (m, 2H), 6.94-6.93 (m, 2H), 6.79 (dd, 1H, $J = 7.4$, 2.0 Hz), 5.88 (s, 1H), 4.55 (s, 2H), 3.61 (s, 3H), 3.39 (t, 2H, $J = 6.9$ Hz), 2.70 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , δ) 165.1, 153.4, 152.7, 148.3, 136.5, 135.4, 131.9, 129.5, 128.7, 128.7, 128.0, 127.7, 124.5, 123.8, 122.7, 122.3, 121, 119.8, 110, 55.5, 49.6, 45.2; IR (ATR) 3328, 1702, 1649 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_3$: 428.1974. Found: 428.1972.



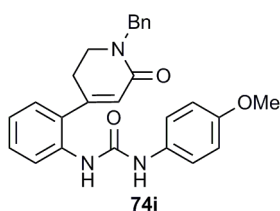
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-(2-chlorophenyl)urea (74g)

A solution of aniline **73** (132 mg, 475 μmol), 2-chlorophenyl isocyanate (69.0 μL , 570 μmol) and DMAP (1.6 mg, 13.1 μmol) in 3 mL of CH_2Cl_2 was heated to 40 $^\circ\text{C}$ for 6 hours in a sealed tube. The reaction mixture was directly subjected to silica gel column chromatography (n -hexane/AcOEt = 8/2 to 6/4) to give the titled compound (192 mg, 94%) as a colorless solid; mp 183-184 $^\circ\text{C}$; ^1H NMR (DMSO- d_6 , δ) 8.74 (s, 1H), 8.53 (s, 1H), 8.09 (d, 1H, $J = 8.3$ Hz), 7.61 (d, 1H, $J = 8.0$ Hz), 7.44 (d, 1H, $J = 8.0$ Hz), 7.32-7.28 (m, 8H), 7.15 (dd, 1H, $J = 7.7, 7.7$ Hz), 7.02 (dd, 1H, $J = 7.7, 7.7$ Hz), 5.92 (s, 1H), 4.59 (s, 2H), 3.47 (t, 2H, $J = 6.9$ Hz), 2.64 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (DMSO- d_6 , δ) 163.7, 152.5, 150.7, 137.7, 136.0, 134.9, 133.0, 129.2, 128.8, 128.4, 128.3, 127.7, 127.5, 127.1, 124.7, 124.2, 123.4, 122.6, 122.2, 121.8, 48.8, 44.9, 28.1; IR (ATR) 3362, 1704, 1644 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{23}^{35}\text{ClN}_3\text{O}_2$: 432.1479. Found: 432.1482.



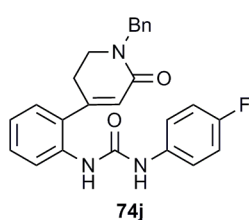
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-(*m*-tolyl)urea (74h)

A solution of aniline **73** (139 mg, 500 μmol), *m*-tolyl isocyanate (70.8 μL , 550 μmol) and DMAP (6.1 mg, 50.0 μmol) in 3 mL of CH_2Cl_2 was stirred for 23 hours at ambient temperature. The reaction mixture was directly evaporated and the residue was washed with Et_2O to give the titled compound (169 mg, 82%) as a colorless solid; mp 162-163 $^\circ\text{C}$; ^1H NMR (DMSO- d_6 , δ) 8.88 (s, 1H), 7.96 (s, 1H), 7.71 (d, 1H, $J = 8.0$ Hz), 7.34-7.09 (m, 11H), 6.77 (d, 1H, $J = 7.4$ Hz), 5.90 (s, 1H), 4.58 (s, 2H), 3.47 (t, 2H, $J = 6.9$ Hz), 2.63 (t, 2H, $J = 6.9$ Hz), 2.25 (s, 3H); ^{13}C NMR (DMSO- d_6 , δ) 152.5, 150.4, 139.6, 137.9, 137.7, 135.3, 131.9, 128.7, 128.6, 128.5, 128.1, 127.8, 127.1, 123.5, 123.4, 122.7, 122.6, 118.6, 115.3, 48.8, 44.8, 28.2, 21.2; IR (ATR) 3270, 1652, 1635 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2$: 412.2025. Found: 412.2034.

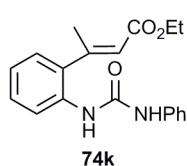


1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-(4-methoxyphenyl)urea (74i)

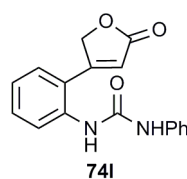
A solution of aniline **73** (139 mg, 500 μmol), 4-methoxyphenyl isocyanate (71.2 μL , 550 μmol) and DMAP (6.1 mg, 50.0 μmol) in 3 mL of CH_2Cl_2 was stirred for 25 hours at ambient temperature. The reaction mixture was directly evaporated and the residue was washed with Et_2O to give the titled compound (204 mg, 95%) as a colorless solid; mp 198-200 $^\circ\text{C}$; ^1H NMR (DMSO- d_6 , δ) 8.77 (brs, 1H), 7.89 (brs, 1H), 7.71 (d, 1H, $J = 8.3$ Hz), 7.33-7.23 (m, 9H), 7.10-7.09 (m, 1H), 6.84 (d, 2H, $J = 8.9$ Hz), 5.89 (s, 1H), 4.58 (s, 2H), 3.70 (s, 3H), 3.47 (t, 2H, $J = 6.9$ Hz), 2.63 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (DMSO- d_6 , δ) 163.7, 154.4, 152.7, 137.7, 135.5, 132.7, 131.8, 128.7, 128.5, 128.1, 127.8, 127.1, 123.3, 123.3, 122.6, 119.9, 114.0, 55.2, 48.8, 44.8, 28.2; IR (ATR) 3255, 1649 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_3$: 428.1974. Found: 428.1973.



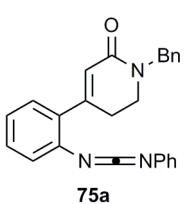
1-(2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-3-(4-fluorophenyl)urea (74j) A solution of aniline **73** (139 mg, 500 μmol), 4-fluorophenyl isocyanate (61.8 μL , 550 μmol) and DMAP (6.1 mg, 50.0 μmol) in 3 mL of CH_2Cl_2 was stirred for 5 hours at ambient temperature. The reaction mixture was directly evaporated and the residue was washed with Et_2O to give the titled compound (204 mg, 98%) as a colorless solid. mp 195-196 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 8.98 (s, 1H), 7.98 (s, 1H), 7.69 (d, 1H, $J = 8.0$ Hz), 7.45-7.42 (m, 2H), 7.34-7.24 (m, 7H), 7.11-7.09 (m, 3H), 5.90 (s, 1H), 4.58 (s, 2H), 3.47 (t, 2H, $J = 6.9$ Hz), 2.64 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , δ) 163.7, 157.3 (d, $J = 236.1$ Hz), 152.7, 150.4, 137.7, 136, 136, 135.2, 132.1, 128.7, 128.5, 128.1, 127.7, 127.1, 123.6, 123.5, 122.6, 119.8 (d, $J = 7.2$ Hz), 115.3 (d, $J = 22.7$ Hz), 48.8, 44.8, 28.1; IR (ATR) 3329, 1700 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2$: 416.1774. Found: 416.1777.



Ethyl (E)-3-(2-(3-Phenylureido)phenyl)but-2-enoate (74k) To a solution of aniline **73k** (85.8 mg, 41.9 μmol) in 2 mL of CH_2Cl_2 , was added PhNCO (47.6 μL , 44.0 μmol). The reaction mixture was stirred at ambient temperature for 3 hours. The mixture was directly subjected to silica gel column chromatography ($\text{CHCl}_3/\text{MeOH} = 95/5$ to 9/1) to give the titled compound (122 mg, 90%) as a colorless solid; mp 160-162 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, δ) 9.02 (s, 1H), 7.86-7.85 (m, 2H), 7.43 (d, 2H, $J = 7.7$ Hz), 7.31-7.25 (m, 3H), 7.15 (d, 1H, $J = 7.4$ Hz), 7.06 (dd, 1H, $J = 7.4$, 7.4 Hz), 6.95 (dd, 1H, $J = 7.4$, 7.4 Hz), 5.82 (s, 1H), 4.14 (q, 2H, $J = 7.0$ Hz), 2.41 (s, 3H), 1.22 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR ($\text{DMSO}-d_6$, δ) 165.5, 155.3, 152.5, 139.7, 135.0, 134.8, 128.8, 128.4, 127.8, 123.0, 122.4, 121.8, 119.9, 118.1, 59.5, 19.9, 14.2; IR (ATR) 3282, 1704, 1645 cm^{-1} , HRMS (MH^+) calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3$: 325.1552. Found: 325.1556.

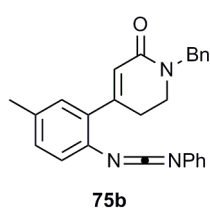


1-(2-(5-Oxo-2,5-dihydrofuran-3-yl)phenyl)-3-phenylurea (74l) A solution of aniline **73l** (86.4 mg, 494 μmol), PhNCO (58.8 μL , 543 μmol), and DMAP (1.1 mg, 9.00 μmol) in 2 mL of CH_2Cl_2 was heated to 40 $^\circ\text{C}$ for 16 hours in a sealed tube. After cooled to ambient temperature, the precipitation was collected by filtration and wash with CH_2Cl_2 to give the titled compound (134 mg, 92%) as a colorless solid; mp 195-197 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, δ) 9.05 (s, 1H), 8.18 (s, 1H), 7.79 (dd, 1H, $J = 8.0$, 1.0 Hz), 7.53-7.45 (m, 4H), 7.28 (ddd, 2H, $J = 7.2$, 7.2, 1.4 Hz), 7.22 (ddd, 1H, $J = 7.6$, 7.6, 1.0 Hz), 6.98 (dd, 1H, $J = 7.4$, 7.4 Hz), 6.53 (t, 1H, $J = 1.7$ Hz), 5.34 (d, 2H, $J = 1.7$ Hz); ^{13}C NMR ($\text{DMSO}-d_6$, δ) 173.7, 163.0, 152.7, 139.6, 137.0, 131.0, 128.8, 128.4, 124.8, 124.1, 123.6, 122.0, 118.3, 115.9, 72.4; IR (ATR) 1629, 1600 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_3$: 295.1083. Found: 295.1081.



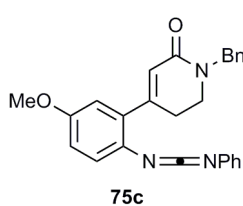
1-Benzyl-4-(2-(((phenylimino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75a) To a solution of urea **74** (55.0 mg, 138 μmol), PPh_3 (55.0 mg, 210 μmol), and Et_3N (55.0 μL , 395 μmol) in 2 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added CBr_4 (55.0 mg, 166 μmol). After an hour the reaction mixture was warmed to ambient temperature. After an

additional hour, the mixture was directly evaporated and the resultant residue was purified by silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3) to give the titled compound (49.3 mg, 94%) as a viscous colorless oil; $^1\text{H NMR}$ (CDCl_3 , δ) 7.36-7.13 (m, 14H), 6.17 (s, 1H), 4.68 (s, 2H), 3.46 (t, 2H, $J = 6.9$ Hz), 2.80 (t, 2H, $J = 6.9$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , δ) 164.8, 150.2, 137.8, 137.4, 135.8, 134.1, 133.9, 129.8, 129.5, 128.9, 128.6, 128.1, 127.4, 125.8, 125.6, 124.2, 123.7, 49.6, 44.8, 28.8; IR (CHCl_3) 2133, 1653 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}$: 380.1763. Found: 380.1762.



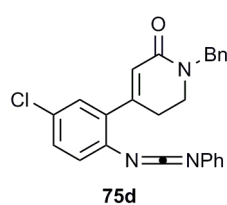
1-Benzyl-4-(5-methyl-2-(((phenylimino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75b) The general procedure using urea **74b** gave the titled compound

(60.2 mg, 90%) as a yellow viscous oil; $^1\text{H NMR}$ (CDCl_3 , δ) 7.34-7.30 (m, 7H), 7.17-7.08 (m, 6H), 6.15 (s, 1H), 4.67 (s, 2H), 3.45 (t, 2H, $J = 6.9$ Hz), 2.79 (t, 2H, $J = 6.9$ Hz), 2.34 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , δ) 164.9, 150.4, 137.4, 135.7, 133.9, 132.9, 130.5, 129.5, 129.5, 128.6, 127.4, 125.7, 125.5, 124.1, 123.5, 49.6, 44.8, 28.9, 20.9; IR (ATR) 2132, 1654, 1486 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}$: 394.1919. Found: 394.1920.



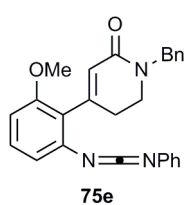
1-Benzyl-4-(5-methoxy-2-(((phenylimino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75c) The general procedure using urea **74c** gave the titled compound

(62.8 mg, 90%) as a yellow viscous oil; $^1\text{H NMR}$ (CDCl_3 , δ) 7.36-7.28 (m, 7H), 7.19-7.11 (m, 4H), 6.86 (dd, 1H, $J = 8.7, 3.0$ Hz), 6.78 (d, 1H, $J = 3.0$ Hz), 6.17 (s, 1H), 4.67 (s, 2H), 3.80 (s, 3H), 3.46 (t, 2H, $J = 7.0$ Hz), 2.80 (t, 2H, $J = 7.0$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , δ) 164.7, 157.3, 150.3, 138.4, 137.4, 135.1, 134.5, 129.5, 128.6, 128.1, 127.4, 126.7, 125.6, 124.1, 123.7, 115.7, 113.6, 55.6, 49.6, 44.8, 28.8; IR (ATR) 2129, 1657, 1485 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_2$: 410.1869. Found: 410.1866.



1-Benzyl-4-(5-chloro-2-(((phenylimino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75d) The general procedure using urea **74d** gave the titled compound

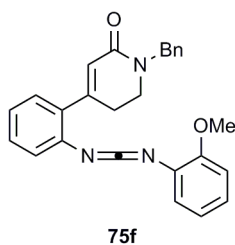
(65.9 mg, 94%) as a yellow viscous oil; $^1\text{H NMR}$ (CDCl_3 , δ) 7.35-7.12 (m, 14H), 6.18 (s, 1H), 4.66 (s, 2H), 3.45 (t, 2H, $J = 7.2$ Hz), 2.76 (t, 2H, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , δ) 164.4, 148.7, 137.3, 135.4, 134.6, 131.0, 129.6, 128.7, 128.6, 128.1, 127.4, 126.7, 126.0, 124.4, 124.3, 49.6, 44.7, 28.6; IR (ATR) 2137, 1656, 1478 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{21}^{35}\text{ClN}_3\text{O}$: 414.1373. Found: 414.1367.



1-Benzyl-4-(2-methoxy-6-(((phenylimino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75e) The general procedure using urea **74e** gave the titled compound

(56.8 mg, 82%) as a yellow viscous oil; $^1\text{H NMR}$ (CDCl_3 , δ) 7.34-7.21 (m, 8H), 7.17 (dd, 1H, $J = 7.6, 7.6$ Hz), 7.12 (dd, 2H, $J = 8.3, 1.0$ Hz), 6.87 (dd, 1H, $J = 8.3, 1.0$ Hz), 6.73 (d, 1H, $J = 8.3$ Hz), 6.02 (s, 1H), 4.61 (s, 2H), 3.79 (s, 3H), 3.40 (t, 2H, $J = 7.0$ Hz), 2.57 (t, 2H, $J = 7.0$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , δ) 164.7, 157.2, 146.2, 138.0, 137.5, 136.5, 129.5, 129.4, 128.6,

128.1, 127.3, 125.6 125.3, 124.2, 124.1, 117.5, 107.8, 55.9, 49.6, 44.7, 28.9; IR (ATR) 2134, 1660, 1467 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_2$: 410.1869. Found: 410.1866.



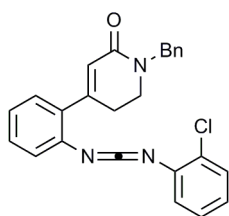
75f

1-Benzyl-4-(2-(((2-methoxyphenyl)imino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75f) The general procedure using urea **74f** gave the titled

compound (56.6 mg, 81%) as a yellow viscous oil; ^1H NMR (CDCl_3 , δ) 7.38-7.26 (m, 8H), 7.15 (dd, 2H, $J = 7.7, 7.7$ Hz), 7.07 (d, 1H, $J = 7.4$ Hz), 6.90 (m, 2H), 6.18 (s, 1H), 4.68 (s, 2H), 3.84 (s, 3H), 3.45 (t, 2H, $J = 6.9$ Hz), 2.83 (t, 2H, $J = 6.9$ Hz);

^{13}C NMR (CDCl_3 , δ) 165.0, 154.0, 150.7, 137.5, 137.1, 135.8, 133.7, 129.7, 128.7,

128.6, 128.1, 127.4, 126.7, 126.5, 125.4, 125.1, 124.8, 123.3, 121.0, 111.0, 56, 49.6, 45.0, 28.8; IR (ATR) 2136, 1654 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_2$: 410.1869. Found: 410.1870.



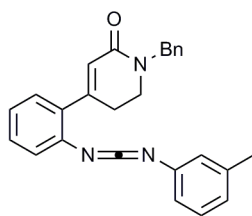
75g

1-Benzyl-4-(2-(((2-chlorophenyl)imino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75g) The general procedure using urea **74g** gave the titled

compound (60.6 mg, 86%) as a colorless amorphus. ^1H NMR (CDCl_3 , δ) 7.41-7.10 (m, 13H), 6.17 (s, 1H), 4.68 (s, 2H), 3.46 (t, 2H, $J = 7.0$ Hz), 2.80 (t, 2H, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , δ) 164.8, 150.2, 142.5, 137.5, 135.4, 135.4, 134.2, 130.0,

129.8, 129.6, 128.9, 128.6, 128.1, 127.7, 127.4, 126.5, 125.9, 125.8, 125.8, 123.7,

49.6, 44.9, 28.9; IR (ATR) 2136, 1651 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{21}^{35}\text{ClN}_3\text{O}$: 414.1373. Found: 414.1373.



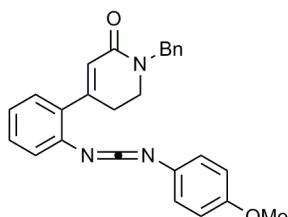
75h

1-Benzyl-4-(2-(((*m*-tolyl)imino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75h) The general procedure using urea **74h** gave the titled compound

(62.7 mg, 94%) as a yellow viscous oil; ^1H NMR (CDCl_3 , δ) 7.34-7.25 (m, 8H), 7.20-7.16 (m, 2H), 6.99 (d, 1H, $J = 7.4$ Hz), 6.95-6.94 (m, 2H), 6.17 (s, 1H), 4.68 (s, 2H), 3.46 (t, 2H, $J = 6.9$ Hz), 2.80 (td, 2H, $J = 6.9, 1.1$ Hz), 2.33 (s, 3H); ^{13}C

NMR (CDCl_3 , δ) 164.8, 150.3, 139.6, 137.6, 137.5, 136.0, 134.1, 134.0, 129.8,

129.3, 129.0, 128.6, 128.1, 127.4, 126.6, 125.7, 125.6, 124.8, 123.7, 121.2, 49.6, 44.9, 28.9, 21.2; IR (ATR) 2132, 1654 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}$: 394.1919. Found: 394.1919.

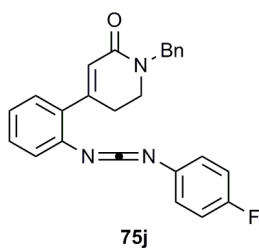


75i

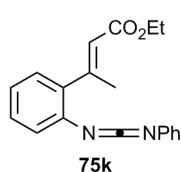
1-Benzyl-4-(2-(((4-methoxyphenyl)imino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75i) The general procedure using urea **74i** gave the

titled compound (61.9 mg, 89%) as a yellow viscous oil; ^1H NMR (CDCl_3 , δ) 7.34-7.24 (m, 8H), 7.17 (dd, 1H, $J = 7.7, 7.7$ Hz), 7.06 (dd, 2H, $J = 6.9, 1.7$ Hz), 6.84 (m, 2H), 6.17 (s, 1H), 4.68 (s, 2H), 3.80 (s, 3H), 3.45 (t, 2H, $J = 6.9$ Hz), 2.80 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , δ) 164.8, 157.6, 150.4, 137.4,

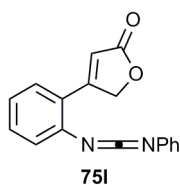
136.4, 134.3, 134.1, 130.1, 129.7, 128.9, 128.6, 128.1, 127.4, 125.6, 125.5, 125.2, 123.6, 114.8, 55.5, 49.6, 44.9, 28.9; IR (ATR) 2128, 1655 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_2$: 410.1869. Found: 410.1871.



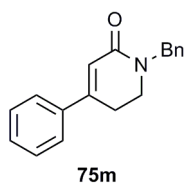
1-Benzyl-4-(2-(((4-fluorophenyl)imino)methylene)amino)phenyl)-5,6-dihydropyridin-2(1H)-one (75j) The general procedure using urea **74j** gave the titled compound (56.3 mg, 83%) as a yellow viscous oil; ^1H NMR (CDCl_3 , δ) 7.32-7.28 (m, 8H), 7.20-7.18 (m, 1H), 7.10-7.08 (m, 2H), 7.01 (dd, 2H, $J = 8.6, 8.6$ Hz), 6.17 (s, 1H), 4.68 (s, 2H), 3.46 (t, 2H, $J = 6.9$ Hz), 2.79 (t, 2H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , δ) 164.8, 160.5 (d, $J = 245.9$ Hz), 150.1, 137.4, 135.6, 134.2, 133.9, 133.8, 133.8, 129.8, 129.0, 128.6, 128.1, 127.4, 125.9, 125.7, 125.53 (d, $J = 8.4$ Hz), 123.8, 116.40 (d, $J = 22.8$ Hz), 49.6, 44.8, 28.9; IR (ATR) 2142, 1657 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{25}\text{H}_{21}\text{FN}_3\text{O}$: 398.1669. Found: 398.1677.



(E)-Ethyl 3-(2-(((Phenylimino)methylene)amino)phenyl)but-2-enoate (75k) To a solution of urea **74k** (55.1 mg, 170 μmol), PPh_3 (66.8 mg, 255 μmol), and Et_3N (52.0 μL , 374 μmol) in 2 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added CBr_4 (67.7 mg, 204 μmol). The reaction mixture was stirred for 2 hours. The mixture was directly evaporated and the resultant residue was purified by silica gel column chromatography (n -hexane/ $\text{Et}_2\text{O} = 10/0$ to 9/1) to give the titled compound (45.4 mg, 87%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.33-7.27 (m, 3H), 7.23 (d, 1H, $J = 7.4$ Hz), 7.18-7.13 (m, 5H), 5.89 (q, 1H, $J = 1.6$ Hz), 4.15 (q, 2H, $J = 7.1$ Hz), 2.54 (d, 3H, $J = 1.6$ Hz), 1.27 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3 , δ) 166.3, 155.5, 138.9, 138.2, 135.1, 129.5, 129.0, 128.6, 125.6, 125.5, 125.3, 124.2, 120.5, 59.9, 20.5, 14.3; IR (ATR) 2141, 1714, 1484 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2$: 307.1447. Found: 307.1447.

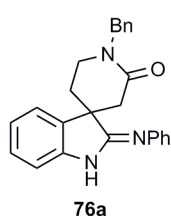


4-(2-(((Phenylimino)methylene)amino)phenyl)furan-2(5H)-one (75l) To a solution of urea **74l** (52.9 mg, 180 μmol), PPh_3 (70.7 mg, 270 μmol), and Et_3N (55.1 μL , 396 μmol) in 1 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added CBr_4 (71.7 mg, 216 μmol). The reaction mixture was stirred for an hour. The mixture was directly evaporated and the resultant residue was purified by silica gel column chromatography (n -hexane/ $\text{AcOEt} = 8/2$ to 7/3) to give the titled compound (36.9 mg, 74%) as a colorless amorphous; ^1H NMR (CDCl_3 , δ) 7.48 (dd, 1H, $J = 8.0, 1.1$ Hz), 7.45-7.42 (m, 1H), 7.38-7.35 (m, 3H), 7.26-7.18 (m, 6H), 6.70 (t, 1H, $J = 1.7$ Hz), 5.40 (d, 2H, $J = 1.7$ Hz); ^{13}C NMR (CDCl_3 , δ) 174.0, 161.5, 138.0, 136.7, 132.1, 129.7, 128.6, 126.5, 126.3, 125.8, 124.4, 124.1, 116.2, 72.7; IR (ATR) 1750, 1718, 1360 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.71; H, 4.61; N, 10.12.

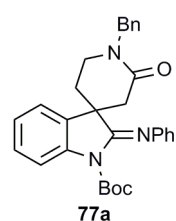


1-Benzyl-4-phenyl-5,6-dihydropyridin-2(1H)-one (75m) A solution of alkenyl triflate **71** (103 mg, 307 μmol), $\text{PhB}(\text{OH})_2$ (56.1 mg, 460 μmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (10.8 mg, 15.4 μmol) in 3 mL of THF and 2 mL of a 2.0 M aqueous Na_2CO_3 solution was heated to reflux for 10 hours. After cooled to ambient temperature, the reaction mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography

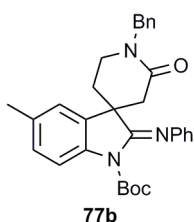
(ⁿhexane/AcOEt = 9/1 to 7/3) to give the titled compound (70.8 mg, 88%) as a colorless solid; mp 103-107 °C; ¹H NMR (CDCl₃, δ) 7.51-7.49 (m, 2H), 7.42-7.27 (m, 8H), 6.38 (t, 1H, *J* = 1.1 Hz), 4.70 (s, 2H), 3.46 (t, 2H, *J* = 7.0 Hz), 2.76 (td, 2H, *J* = 7.1, 1.2 Hz); ¹³C NMR (CDCl₃, δ) 165.2, 149.3, 137.30, 137.26, 129.4, 128.7, 128.5, 127.9, 127.3, 125.6, 119.6, 49.4, 44.5, 26.4; IR (ATR) 2923, 1649, 1605, 1481, 1446 cm⁻¹; HRMS (MH⁺) calcd for C₁₈H₁₈NO: 264.1389. Found: 264.1382.



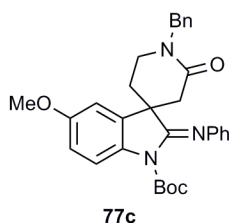
1'-Benzyl-2-(phenylimino)spiro[indoline-3,4'-piperidin]-2'-one (76a) To a solution of SmI₂ (0.1 M in THF, 2.4 mL, 240 μmol), was added a solution of carbodiimide **75** (37.9 mg, 100 μmol) and ^tBuOH (21.0 μL, 220 μmol) in 2 mL of THF in a dropwise manner. After 15 minutes, a saturated aqueous NH₄Cl solution was added and the organic solvent was removed by evaporation. This aqueous solution was extracted with AcOEt. The organic layer was extracted with a 1 M aqueous HCl solution and the resultant aqueous layer was neutralized with solid NaHCO₃. This aqueous layer was extracted with AcOEt and the organic layer was dried over Na₂SO₄, concentrated under reduced pressure, and dried in vacuo. The crude material was purified by silica gel column chromatography (ⁿhexane/AcOEt = 8/2 to 6/4) to give the titled compound (31.5 mg, 83%) as a colorless solid; mp 176-177 °C; ¹H NMR (CDCl₃, δ) 7.38-7.29 (m, 20H), 7.16-7.09 (m, 2H), 6.95-6.94 (m, 3H), 6.86-6.82 (m, 2H), 6.68 (d, 1H, *J* = 8.0 Hz), 4.88 (d, 1H, *J* = 14.3 Hz), 4.68 (d, 1H, *J* = 14.3 Hz), 3.69-3.65 (m, 1H), 3.47-3.44 (m, 1H), 3.10 (d, 1H, *J* = 17.5 Hz), 2.69 (d, 1H, *J* = 17.5 Hz), 2.33-2.27 (m, 1H), 1.99-1.97 (m, 1H); ¹³C NMR (CDCl₃, δ) 168.1, 162.7, 149.2, 141.6, 136.8, 132.1, 129.6, 128.6, 128.5, 128.4, 127.5, 123.6, 123.5, 121.5, 121.3, 108.9, 50.2, 46.8, 43.2, 40.8, 32.3; IR (ATR) 3144, 1662, 1625 cm⁻¹; MS (FAB⁺) *m/z* = 382 (MH⁺); Anal. Calcd for C₂₅H₂₃N₃O: C, 78.71; H, 6.08; N, 11.02. Found: C, 78.55; H, 6.08; N, 10.70.



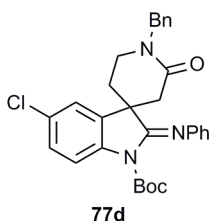
tert-Butyl 1'-Benzyl-2'-oxo-2-(phenylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77a) To a solution of iminoindoline **76a** (38.1 mg, 100 μmol) in 1 mL of CH₂Cl₂, was added Boc₂O (32.7 mg, 150 μmol) in 1 mL of CH₂Cl₂. Then DMAP (12.2 mg, 100 μmol) was added. After 5 hours the reaction mixture was directly subjected to silica gel column chromatography (ⁿhexane/AcOEt = 6/4) to give the titled compound (47.1 mg, 98%) as a colorless solid; mp 163-165 °C; ¹H NMR (CDCl₃, δ) 7.65 (d, 1H, *J* = 8.0 Hz), 7.41-7.25 (m, 9H), 7.08-7.08 (m, 2H), 7.03 (dd, 1H, *J* = 7.4, 7.4 Hz), 6.86 (d, 2H, *J* = 6.9 Hz), 5.00 (d, 1H, *J* = 14.3 Hz), 4.51 (d, 1H, *J* = 14.3 Hz), 3.72-3.67 (m, 1H), 3.35-3.30 (m, 1H), 3.06 (m, 1H), 2.76 (d, 1H, *J* = 17.8 Hz), 2.18-2.13 (m, 1H), 2.06-2.01 (m, 1H), 1.15 (s, 9H); ¹³C NMR (CDCl₃, δ) 168.3, 155.8, 149.2, 148.3, 140.4, 136.8, 132.5, 128.9, 128.7, 128.6, 128.4, 127.4, 124.3, 123.7, 122.6, 120.5, 114.8, 83.8, 50.5, 47.5, 43.3, 39.6, 32.8, 27.4; IR (ATR) 1727, 1704, 1625 cm⁻¹; The structure of **77a** was established by X-ray crystallography. Crystallographic data reported have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-847381. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U. K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).



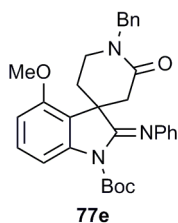
tert-Butyl 1'-Benzyl-5-methyl-2'-oxo-2-(phenylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77b) The general procedure (condition A) using carbodiimide **75b** give the titled compound (43.3 mg, 2 steps, 87%) as a colorless solid; mp 152-154 °C; ¹H NMR (CDCl₃, δ) 7.52 (d, 1H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 7.4 Hz), 7.36 (dd, 2H, *J* = 7.4, 7.4 Hz), 7.32 (d, 1H, *J* = 7.4 Hz), 7.27 (dd, 2H, *J* = 7.4, 7.4 Hz), 7.07 (d, 1H, *J* = 7.4 Hz), 7.02 (t, 1H, *J* = 7.4 Hz), 6.86 (d, 2H, *J* = 8.0 Hz), 6.83 (s, 1H), 4.80 (d, 1H, *J* = 14.3 Hz), 4.71 (d, 1H, *J* = 14.3 Hz), 3.67-3.62 (m, 1H), 3.36-3.32 (m, 1H), 3.08 (d, 1H, *J* = 17.2 Hz), 2.72 (d, 1H, *J* = 17.2 Hz), 2.25 (s, 3H), 2.18-2.16 (m, 1H), 2.03-1.99 (m, 1H), 1.15 (s, 9H); ¹³C NMR (CDCl₃, δ) 168.3, 156.1, 149.3, 148.4, 138.0, 136.8, 134.0, 132.4, 129.0, 128.9, 128.6, 128.5, 127.4, 123.6, 123.3, 120.4, 114.6, 83.6, 50.5, 47.5, 43.4, 39.6, 32.7, 27.4, 21.0; IR (ATR) 1738, 1700, 1640 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₃₄N₃O₃: 496.2600. Found: 496.2604.



tert-Butyl 1'-Benzyl-5-methoxy-2'-oxo-2-(phenylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77c) The general procedure (condition A) with carbodiimide **75c** gave the titled compound (37.6 mg, 2 steps, 73%) as a colorless solid; mp 158-161 °C; ¹H NMR (CDCl₃, δ) 7.57 (d, 1H, *J* = 8.6 Hz), 7.41-7.26 (m, 8H), 7.03 (t, 1H, *J* = 7.2 Hz), 6.87-6.81 (m, 3H), 6.68 (s, 1H), 4.98 (d, 1H, *J* = 14.6 Hz), 4.52 (d, 1H, *J* = 14.6 Hz), 3.73-3.71 (m, 4H), 3.36-3.34 (m, 1H), 3.06 (d, 1H, *J* = 17.8 Hz), 2.75 (d, 1H, *J* = 17.8 Hz), 2.15-2.14 (m, 1H), 2.06-2.03 (m, 1H), 1.14 (s, 9H); ¹³C NMR (CDCl₃, δ) 168.2, 156.9, 156.0, 149.3, 148.3, 136.8, 133.9, 133.7, 128.9, 128.7, 128.4, 127.4, 123.7, 120.5, 115.8, 113.2, 109.1, 83.6, 55.7, 50.5, 47.9, 43.4, 39.5, 32.8, 27.5; IR (ATR) 1723, 1698, 1640 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₃₄N₃O₄: 512.2549. Found: 512.2554.

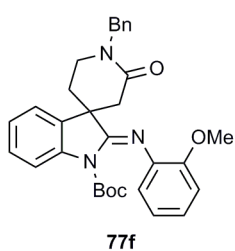


tert-Butyl 1'-Benzyl-5-chloro-2'-oxo-2-(phenylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77d) The general procedure (condition A) using carbodiimide **75d** gave the titled compound (32.0 mg, 2 steps, 62%) as a colorless oil; ¹H NMR (CDCl₃, δ) 7.59 (d, 1H, *J* = 8.6 Hz), 7.41-7.35 (m, 4H), 7.33-7.24 (m, 4H), 7.06-7.02 (m, 2H), 6.85 (dd, 2H, *J* = 8.6 Hz), 4.88 (d, 1H, *J* = 14.6 Hz), 4.63 (d, 1H, *J* = 14.6 Hz), 3.70-3.65 (m, 1H), 3.34-3.29 (m, 1H), 3.07 (d, 1H, *J* = 17.8 Hz), 2.72 (d, 1H, *J* = 17.8 Hz), 2.20-2.15 (m, 1H), 2.04-1.99 (m, 1H), 1.14 (s, 9H); ¹³C NMR (CDCl₃, δ) 167.8, 154.9, 149.0, 148.0, 138.9, 136.7, 134.3, 129.7, 129.0, 128.7, 128.7, 128.3, 127.5, 123.9, 123.0, 120.5, 116.0, 84.2, 50.5, 47.7, 43.2, 39.5, 32.6, 27.4; IR (ATR) 1726, 1698, 1640 cm⁻¹; HRMS (MH⁺) calcd for C₃₀H₃₁³⁵ClN₃O₃: 516.2054. Found: 516.2057.



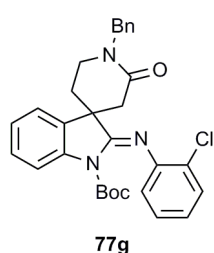
tert-Butyl 1'-Benzyl-5-methoxy-2'-oxo-2-(phenylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77e) The general procedure (condition A) using carbodiimide **75e** give the titled compound (38.3 mg, 2 steps, 75%) as a colorless solid; mp 161-162 °C; ¹H NMR (CDCl₃, δ) 7.40 (d, 2H, *J* = 6.9 Hz), 7.32-7.26 (m, 7H), 7.01 (t, 1H, *J* = 7.2 Hz), 6.80 (d, 2H, *J* = 7.4 Hz), 6.69 (d, 1H, *J* = 8.0 Hz), 5.19 (d, 1H, *J* = 14.6 Hz), 4.29 (d, 1H,

$J = 14.6$ Hz), 3.87-3.81 (m, 4H), 3.48 (d, 1H, $J = 17.8$ Hz), 3.25-3.23 (m, 1H), 2.82 (d, 1H, $J = 17.8$ Hz), 2.57-2.53 (m, 1H), 1.93-1.90 (m, 1H), 1.12 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 169.4, 156.1, 149.3, 148.5, 141.7, 137.1, 129.6, 128.9, 128.6, 128.2, 127.1, 123.6, 120.5, 118.8, 107.5, 107.0, 99.9, 83.8, 55.4, 50.7, 48.2, 43.4, 37.4, 29.9, 27.4; IR (ATR) 1727, 1704, 1625 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_3\text{O}_4$: 512.2549. Found: 512.2547.



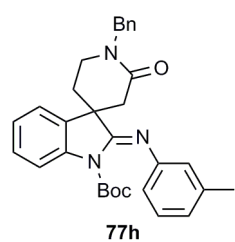
tert-Butyl 1'-Benzyl-2-((2-methoxyphenyl)imino)-2'-oxospiro[indoline-3,4'-piperidine]-1-carboxylate (77f) The general procedure (condition B) using carbodiimide **75f** gave the titled compound (33.6 mg, 2 steps, 66%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.68 (d, 1H, $J = 8.0$ Hz), 7.36-7.29 (m, 5H), 7.06 (m, 2H), 7.01 (ddd, 1H, $J = 7.7, 7.7, 1.7$ Hz), 6.88 (dd, 1H, $J = 7.6, 7.6$ Hz), 6.84 (d, 1H, $J = 8.0$ Hz), 6.79 (dd, 1H, $J = 7.7, 1.4$ Hz), 4.82 (d, 1H, $J = 14.6$ Hz), 4.68 (d, 1H, $J = 14.6$ Hz),

3.78-3.72 (m, 4H), 3.36-3.31 (m, 1H), 3.08 (d, 1H, $J = 17.5$ Hz), 2.74 (d, 1H, $J = 17.5$ Hz), 2.24-2.18 (m, 1H), 2.05-2.00 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 168.5, 155.1, 149.6, 149.3, 140.6, 137.4, 137.0, 132.5, 128.6, 128.5, 128.4, 127.4, 124.2, 123.9, 122.7, 121.7, 120.7, 114.3, 111.2, 83.5, 55.5, 50.3, 47.7, 43.3, 40.1, 33.0, 27.4; IR (ATR) 1720, 1699, 1658 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_3\text{O}_4$: 512.2549. Found: 512.2552.



tert-Butyl 1'-Benzyl-2-((2-chlorophenyl)imino)-2'-oxospiro[indoline-3,4'-piperidine]-1-carboxylate (77g) The general procedure (condition B) using carbodiimide **75g** gave the titled compound (44.6 mg, 2 steps, 86%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.63 (d, 1H, $J = 8.0$ Hz), 7.38-7.26 (m, 7H), 7.17-7.10 (m, 3H), 6.97 (dd, 1H, $J = 8.0, 7.4$ Hz), 6.85 (d, 1H, $J = 8.0$ Hz), 4.96 (d, 1H, $J = 14.6$ Hz), 4.54 (d, 1H, $J = 14.6$ Hz), 3.88-3.83 (m, 1H), 3.36-3.32 (m, 1H), 3.04 (d, 1H, $J = 17.5$ Hz), 2.81 (d, 1H,

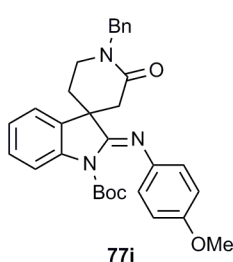
$J = 17.5$ Hz), 2.21-2.16 (m, 1H), 2.08-2.03 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 168.2, 156.9, 149.0, 145.8, 140.1, 137.0, 132.3, 129.8, 128.7, 128.6, 128.4, 127.4, 127.1, 125.6, 124.3, 124.2, 122.6, 120.3, 114.5, 84.3, 50.2, 47.9, 43.1, 40.0, 33.0, 27.5; IR (ATR) 1730, 1701, 1646 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{20}\text{H}_{31}^{35}\text{ClN}_3\text{O}_3$: 516.2054. Found: 516.2060.



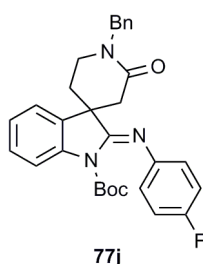
tert-Butyl 1'-Benzyl-2'-oxo-2-(m-tolylimino)spiro[indoline-3,4'-piperidine]-1-carboxylate (77h) The general procedure (condition B) using carbodiimide **75h** gave the titled compound (40.0 mg, 2 steps, 81%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.66 (d, 1H, $J = 8.0$ Hz), 7.41-7.08 (m, 9H), 6.85 (d, 1H, $J = 7.4$ Hz), 6.68-6.67 (m, 2H), 5.05 (d, 1H, $J = 14.3$ Hz), 4.47 (d, 1H, $J = 14.3$ Hz), 3.73-3.68 (m, 1H), 3.34-3.30 (m, 1H), 3.05 (d, 1H, $J = 17.5$ Hz), 2.77 (d, 1H, $J = 17.5$ Hz), 2.31 (s, 3H),

2.18-2.13 (m, 1H), 2.06-2.03 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 168.3, 155.5, 149.3, 148.2, 140.5, 138.6, 136.8, 132.5, 128.8, 128.7, 128.6, 128.4, 127.4, 124.5, 124.2, 122.6, 121.3, 117.3, 114.7, 83.8, 50.5, 47.5, 43.3, 39.7, 32.8, 27.4, 21.3; IR (ATR) 1724, 1697, 1644 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_3\text{O}_3$:

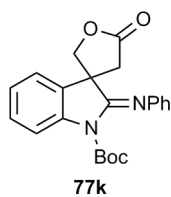
496.2600. Found: 496.2603.



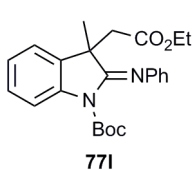
tert-Butyl 1'-Benzyl-2-((4-methoxyphenyl)imino)-2'-oxospiro[indoline-3,4'-piperidine]-1-carboxylate (77i) The general procedure (condition B) using carbodiimide **75i** gave the titled compound (38.1 mg, 2 steps, 74%) as a colorless solid; mp 157-158 °C; ^1H NMR (CDCl_3 , δ) 7.65 (d, 1H, $J = 8.0$ Hz), 7.42-7.26 (m, 7H), 7.09-7.08 (m, 2H), 6.83 (m, 3H), 5.01 (d, 1H, $J = 14.3$ Hz), 4.50 (d, 1H, $J = 14.3$ Hz), 3.78 (s, 3H), 3.71-3.65 (m, 1H), 3.33-3.29 (m, 1H), 3.05 (d, 1H, $J = 17.8$ Hz), 2.76 (d, 1H, $J = 17.8$ Hz), 2.15-2.11 (m, 1H), 2.04-2.00 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 168.4, 156.3, 155.0, 149.4, 141.6, 140.5, 136.8, 132.7, 128.6, 128.6, 128.4, 127.4, 124.2, 122.6, 121.8, 115.0, 114.2, 83.6, 55.5, 50.4, 47.5, 43.3, 39.6, 32.8, 27.5; IR (ATR) 1722, 1694, 1637 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_3\text{O}_4$: 512.2549. Found: 512.2551.



tert-Butyl 1'-Benzyl-2-((4-fluorophenyl)imino)-2'-oxospiro[indoline-3,4'-piperidine]-1-carboxylate (77j) The general procedure (condition B) using carbodiimide **75j** gave the titled compound (43.7 mg, 2 steps, 87%) as a colorless solid; mp 174-177 °C; ^1H NMR (CDCl_3 , δ) 7.62 (d, 1H, $J = 8.0$ Hz), 7.41-7.26 (m, 8H), 7.10-7.09 (m, 2H), 6.99-6.96 (m, 2H), 6.80-6.78 (m, 2H), 5.04 (d, 1H, $J = 14.3$ Hz), 4.47 (d, 1H, $J = 14.3$ Hz), 3.71-3.66 (m, 1H), 3.34-3.29 (m, 1H), 3.03 (d, 1H, $J = 17.5$ Hz), 2.77 (d, 1H, $J = 17.5$ Hz), 2.16-2.11 (m, 1H), 2.07-2.01 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 168.2, 159.4 (d, $J = 242.3$ Hz), 156.3, 149.1, 144.5 (d, $J = 2.4$ Hz), 140.3, 136.8, 132.5, 128.8, 128.7, 128.4, 127.4, 124.4, 122.7, 121.7 (d, $J = 7.2$ Hz), 115.5 (d, $J = 21.6$ Hz), 114.9, 84.0, 50.5, 47.6, 43.3, 39.6, 32.8, 27.6; IR (ATR) 1725, 1699, 1638 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{30}\text{H}_{31}\text{FN}_3\text{O}_3$: 500.2350. Found: 500.2352.

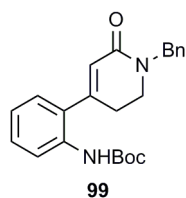


tert-Butyl 5-Oxo-2'-(phenylimino)-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-1-carboxylate (77k) The general procedure (condition B) using carbodiimide **75k** gave the titled compound (31.5 mg, 2 steps, 83%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.69 (d, 1H, $J = 8.0$ Hz), 7.38-7.30 (m, 4H), 7.21 (dd, 1H, $J = 7.4, 7.4$ Hz), 7.07 (t, 1H, $J = 7.4$ Hz), 6.98 (d, 2H, $J = 7.4$ Hz), 4.76 (d, 1H, $J = 8.9$ Hz), 4.45 (d, 1H, $J = 8.9$ Hz), 3.29 (d, 1H, $J = 17.5$ Hz), 2.87 (d, 1H, $J = 17.5$ Hz), 1.19 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 174.6, 153.9, 148.9, 147.8, 140.9, 130.3, 129.5, 129.1, 124.1, 122.1, 120.4, 114.7, 84.6, 76.7, 51.9, 40.8, 27.4; IR (ATR) 1785, 1728, 1698 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_4$: 379.1658. Found: 379.1659.



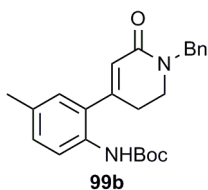
tert-Butyl 3-(2-Ethoxy-2-oxoethyl)-3-methyl-2-(phenylimino)indoline-1-carboxylate (77l) The general procedure (condition B) using carbodiimide **75l** gave the titled compound (31.0 mg, 2 steps, 76%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.64 (d, 1H, $J = 8.0$ Hz), 7.29-7.26 (m, 3H), 7.18 (d, 1H, $J = 6.9$ Hz), 7.10 (t, 1H, $J = 7.4$ Hz), 7.00-6.99 (m, 3H), 3.97-3.84 (m, 2H), 3.20 (d, 1H, $J = 16.6$ Hz), 2.89 (d, 1H, $J = 16.6$ Hz), 1.25 (s, 9H),

1.00 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , δ) 170.0, 158.2, 149.5, 141.1, 134.1, 128.9, 128.0, 123.7, 123.0, 121.7, 120.1, 114.2, 83.5, 60.3, 46.7, 43.4, 27.6, 27.3, 13.9; IR (ATR) 1730, 1699 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4$: 409.2127. Found: 409.2125.



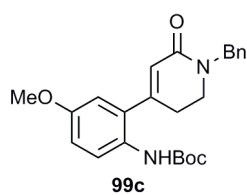
***tert*-Butyl (2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl)carbamate (99)**

A solution of boronic acid **98** (16.3 g, 68.8 mmol), alkenyl triflate **71** (19.2 g, 57.3 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (2.01 g, 2.87 mmol) in 150 mL of THF and 150 mL of a 2.0 M aqueous Na_2CO_3 solution was heated to reflux for an hour. The reaction mixture was cooled to ambient temperature. The aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 8/2 to 4/6) to give the titled compound (19.0 g, 88%) as a colorless solid; mp 171-172 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.84 (d, 1H, $J = 8.6$ Hz), 7.34-7.32 (m, 6H), 7.14-7.08 (m, 2H), 6.49 (s, 1H), 6.09 (s, 1H), 4.69 (s, 2H), 3.47 (t, 2H, $J = 7.2$ Hz), 2.63 (t, 2H, $J = 7.2$ Hz), 1.49 (s, 9H). ^{13}C NMR (CDCl_3 , δ) 164.3, 152.9, 149.4, 137.2, 134.3, 130.8, 129.3, 128.7, 128.2, 127.6, 127.5, 124.0, 123.8, 122.0, 80.9, 49.7, 44.8, 29.1, 28.3; IR (ATR) 3160, 1709, 1656 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3$: 379.2022. Found: 379.2020.

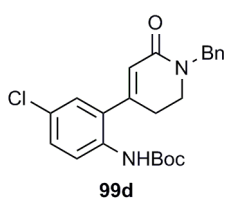


***tert*-Butyl (2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-methylphenyl)carbamate (99b)**

To a solution of *N*-Boc *p*-toluidine (217 mg, 1.05 mmol) in 4 mL of Et_2O at -78 $^\circ\text{C}$, was added $^t\text{BuLi}$ (1.76 M in pentane, 1.43 mL, 2.52 mmol) in a dropwise manner. The reaction mixture was stirred at the same temperature for 15 minutes and warmed to -20 $^\circ\text{C}$. After 3 hours trimethoxyborane (445 μL , 3.99 mmol) was added. The reaction mixture was warmed to ambient temperature and stirred for 20 minutes. To the mixture, was added a 2.0 M aqueous HCl solution to pH 7. The organic layer was separated and the aqueous layer was extracted with CHCl_3 . The combined organic layers were washed with a saturated aqueous NaHCO_3 solution and dried over Na_2SO_4 . Concentration under reduced pressure gave 252 mg of a pale yellow amorphous. The amorphous and alkenyl triflate **71** (387 mg, 1.16 mmol) was dissolved in 10 mL of THF and 10 mL of a 2.0 M aqueous Na_2CO_3 solution and $\text{PdCl}_2(\text{PPh}_3)_2$ (73.7 mg, 105 μmol) was added to the solution. The mixture was heated to reflux for 13 hours. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 7/3 to 6/4) to give the titled compound (262 mg, 2 steps, 64%) as a colorless solid; mp 159-160 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.64 (d, 1H, $J = 6.9$ Hz), 7.37-7.27 (m, 5H), 7.11 (dd, 1H, $J = 8.3, 1.4$ Hz), 6.95 (d, 1H, $J = 1.4$ Hz), 6.42 (br s, 1H), 6.06 (s, 1H), 4.68 (s, 2H), 3.45 (t, 2H, $J = 7.0$ Hz), 2.62 (t, 2H, $J = 7.0$ Hz), 2.30 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (CDCl_3 , δ) 164.5, 153.1, 149.8, 137.2, 133.8, 131.6, 129.8, 128.6, 128.1, 127.5, 123.4, 122.7, 80.6, 49.6, 44.8, 29.0, 28.3, 20.7; IR (ATR) 3317, 1684, 1657 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_3$: 393.2178. Found: 393.2175.

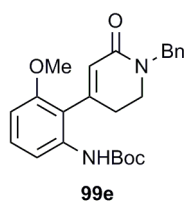


tert-Butyl (2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-methoxyphenyl)carbamate (99c) To a solution of *N*-Boc *p*-anisidine (335 mg, 1.50 mmol) in 5 mL of Et₂O at -78 °C, was added ^tBuLi (1.76 M in pentane, 2.05 mL) in a dropwise manner. The reaction mixture was stirred at the same temperature for 15 minutes and warmed to -20 °C. After 2.5 hours trimethoxyborane (636 μL, 3.99 mmol) was added. The mixture was warmed to ambient temperature and stirred for 13 hours. To the mixture, was added a 2.0 M aqueous HCl solution to pH 7. The organic layer was separated and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with a saturated aqueous NaHCO₃ solution and dried over Na₂SO₄. Concentration under reduced pressure gave 392 mg of a pale yellow amorphus. The amorphus and alkenyl triflate **71** (503 mg, 1.50 mmol) was dissolved in 10 mL of THF and 10 mL of a 2.0 M aqueous Na₂CO₃ solution and PdCl₂(PPh₃)₂ (105 mg, 0.150 mmol) was added to the solution. The mixture was heated to reflux for 1 hour. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/AcOEt = 6/4 to 5/5) to give the titled compound (419 mg, 2 steps, 68%) as a colorless solid; mp 132-133 °C; ¹H NMR (CDCl₃, δ) 7.50 (s, 1H), 7.35-7.27 (m, 5H), 6.84 (dd, 1H, *J* = 8.9, 2.9 Hz), 6.69 (d, 1H, *J* = 2.9 Hz), 6.40 (br, 1H), 6.05 (s, 1H), 4.67 (s, 2H), 3.77 (s, 3H), 3.44 (t, 2H, *J* = 7.2 Hz), 2.62 (t, 2H, *J* = 7.2 Hz), 1.45 (s, 9H). ¹³C NMR (CDCl₃, δ) 164.4, 156.6, 153.6, 149.8, 149.8, 137.2, 128.6, 128.1, 127.4, 127.1, 123.4, 114.4, 113.0, 80.4, 55.5, 49.6, 44.8, 28.7, 28.2; IR (ATR) 3264, 1712, 1655 cm⁻¹; HRMS (MH⁺) calcd for C₂₄H₂₉N₂O₄: 409.2127. Found: 409.2122.



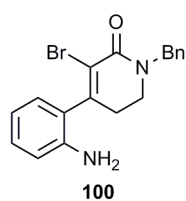
tert-Butyl (2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-4-chlorophenyl)carbamate (99d) To a solution of *N*-Boc 4-chloroaniline (342 mg, 1.50 mmol) in 6 mL of Et₂O at -78 °C, was added ^tBuLi (1.76 M in pentane, 2.05 mL) in a dropwise manner. The reaction mixture was stirred at the same temperature for 15 minutes and warmed to -20 °C. After 1.5 hours trimethoxyborane (636 μL, 3.99 mmol) was added. The mixture was warmed to ambient temperature and stirred for 12 hours. To the mixture, was added a 2.0 M aqueous HCl solution to pH 7. The organic layer was separated and the aqueous layer was extracted with CHCl₃. The combined organic layers were washed with a saturated aqueous NaHCO₃ solution and dried over Na₂SO₄. Concentration under reduced pressure gave 377 mg of a pale yellow amorphus. The amorphus and alkenyl triflate **71** (553 mg, 1.65 mmol) was dissolved in 10 mL of THF and 10 mL of a 2 M aqueous Na₂CO₃ solution and PdCl₂(PPh₃)₂ (105 mg, 150 μmol) was added to the solution. The mixture was heated to reflux for 18 hours. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/AcOEt = 8/2 to 7/3) to give the titled compound (389 mg, 2 steps, 64%) as a colorless solid; mp 162-163 °C; ¹H NMR (CDCl₃, δ) 7.82 (d, 1H, *J* = 8.3 Hz), 7.37-7.25 (m, 6H), 7.12 (d, 1H, *J* = 2.6 Hz), 6.55 (br, 1H), 6.08 (s, 1H), 4.68 (s, 2H), 3.47 (t, 2H, *J* = 7.0 Hz), 2.60 (t, 2H, *J* = 7.0 Hz), 1.48 (s, 9H). ¹³C NMR (CDCl₃, δ)

164.0, 152.7, 148.0, 137.0, 133.0, 132.0, 129.1, 129.1, 128.7, 128.1, 127.6, 127.4, 124.4, 123.2, 81.2, 49.7, 44.7 28.8, 28.2; IR (ATR) 3240, 1715, 1655 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{23}\text{H}_{26}^{35}\text{ClN}_2\text{O}_3$: 413.1632. Found: 4113.1631.



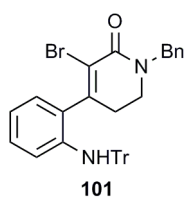
tert-Butyl (2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)-3-methoxyphenyl)carbamate (99e)

To a solution of *N*-Boc *m*-anisidine (669 mg, 3.00 mmol) in 12 mL of Et_2O at -78°C , was added $t\text{BuLi}$ (1.76 M in pentane, 4.09 mL) in a dropwise manner. The reaction mixture was stirred at the same temperature for 15 minutes and warmed to -20°C . After 23 hours trimethoxyborane (1.17 mL, 10.5 mmol) was added. The mixture was warmed to ambient temperature and stirred for 1.5 hours. To the mixture, was added a 2.0 M aqueous HCl solution to pH 3. The organic layer was separated and the aqueous layer was extracted with CHCl_3 . The combined organic layers were washed with a saturated aqueous NaHCO_3 solution and dried over Na_2SO_4 . Concentration under reduced pressure gave 603 mg of a pale yellow amorphus. The amorphus and alkenyl triflate **71** (503 mg, 1.50 mmol) was dissolved in 10 mL of THF and 10 mL of a 2.0 M aqueous Na_2CO_3 solution and $\text{PdCl}_2(\text{PPh}_3)_2$ (52.7 mg, 75.0 μmol) was added to the solution. The mixture was heated to reflux for 13 hours. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ($n\text{hexane}/\text{AcOEt} = 8/2$ to $6/4$) to give the titled compound (445 mg, 2 steps, 73%) as a colorless solid; mp $154\text{--}155^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.64 (d, 1H, $J = 8.3$ Hz), 7.36–7.23 (m, 5H), 6.62–6.61 (m, 2H), 5.97 (s, 1H), 4.70 (brs, 2H), 3.77 (s, 3H), 3.46 (t, 2H, $J = 6.9$ Hz), 2.55 (brs, 2H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 164.4, 156.3, 152.7, 147.6, 137.2, 135.2, 129.5, 128.6, 128.2, 127.4, 124.9, 118.6, 112.9, 105.6, 80.8, 55.7, 49.8, 45.0, 28.7, 28.3; IR (ATR) 3171, 1713, 1651 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4$: 409.2127. Found: 409.2135.



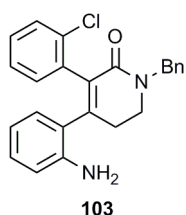
4-(2-Aminophenyl)-1-benzyl-3-bromo-5,6-dihydropyridin-2(1H)-one (100)

To a solution of *N*-Boc aniline **99** (567 mg, 1.50 mmol) in 10 mL of CCl_4 at 0°C , was added bromine (84.6 μL , 1.65 mmol) in a dropwise manner. After 10 minutes, the reaction mixture was directly evaporated and this residue was dissolved in 10 mL of dioxane. After the mixture was cooled to 0°C , DBU (447 μL , 3.00 mmol) was added in a dropwise manner. After 20 minutes, a saturated aqueous NH_4Cl solution was added and the separated aqueous layer was extracted with CHCl_3 . The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ($n\text{hexane}/\text{AcOEt} = 8/2$ to $6/4$) to give the titled compound (450 mg, 84%) as a brown solid; mp $66\text{--}68^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.37–7.28 (m, 5H), 7.16 (m, 1H), 6.95 (dd, 1H, $J = 7.5, 1.5$ Hz), 6.80 (m, 1H), 6.75 (d, 1H, $J = 8.0$ Hz), 4.76 (d, 1H, $J = 14.3$ Hz), 4.67 (d, 1H, $J = 14.3$ Hz), 3.66 (brs, 2H), 3.47 (t, 2H, $J = 6.9$ Hz), 2.70–2.59 (m, 2H); ^{13}C NMR (CDCl_3 , δ) 160.4, 149.0, 141.7, 136.8, 129.6, 128.7, 128.2, 127.7, 127.3, 125.9, 118.7, 118.4, 116.2, 51.3, 44.4, 31.4; IR (ATR) 3420, 3342, 1635 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{18}\text{H}_{18}^{79}\text{BrN}_2\text{O}$: 357.0603. Found: 357.0601.



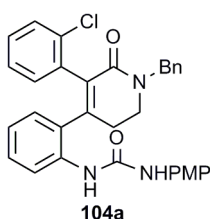
1-Benzyl-3-bromo-4-[2-(tritylamino)phenyl]-5,6-dihydropyridin-2(1H)-one (101) To a solution of bromolactam **100** (4.64 g, 13.0 mmol) and Et₃N (18.1 mL, 130 mmol) in 100 mL of CH₂Cl₂ at 0 °C, was added TrCl (21.7 g, 78.0 mmol) in two portions. The reaction mixture was warmed to ambient temperature and stirred for 5 hours. Then a saturated aqueous NaHCO₃ solution was added and the separated organic layer was

washed with water and a saturated aqueous NaHCO₃ solution, dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ("hexane/AcOEt = 9/1 to 7/3) to give the titled compound (6.16 g, 79%) as a colorless solid; mp 201-203 °C; ¹H NMR (CDCl₃, δ) 7.35-7.19 (m, 20H), 6.89 (dd, 1H, *J* = 7.4, 1.7 Hz), 6.77 (m, 1H), 6.63 (m, 1H), 6.14 (d, 1H, *J* = 8.0 Hz), 4.91 (s, 1H), 4.73 (d, 1H, *J* = 14.3 Hz), 4.67 (d, 1H, *J* = 14.3 Hz), 3.46-3.33 (m, 2H), 2.68-2.67 (m, 2H); ¹³C NMR (CDCl₃, δ) 160.3, 149.2, 140.9, 136.8, 128.8, 128.7, 128.2, 128.1, 128.0, 127.9, 127.7, 127.1, 127.0, 126.4, 119.9, 117.2, 116.0, 71.0, 51.2, 44.5, 31.5; IR (ATR) 3431, 1651 cm⁻¹; HRMS (MH⁺) calcd for C₃₇H₃₂⁸¹BrN₂O: 601.1678. Found: 601.1677.



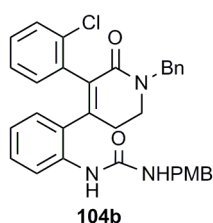
4-(2-Aminophenyl)-1-benzyl-3-(2-chlorophenyl)-5,6-dihydropyridin-2(1H)-one (103)

A solution of *N*-trityl aniline **101** (300 mg, 500 μmol), 2-chlorophenyl boronic acid (235 mg, 1.50 mmol), and PdCl₂(PPh₃)₂ (17.5 mg, 25.0 μmol) in 10 mL of dioxane and 10 mL of a 2.0 M aqueous Na₂CO₃ solution was heated to reflux for an hour. The reaction mixture was cooled to ambient temperature. The separated aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. This crude material was dissolved in 9.5 mL of CH₂Cl₂ and the resultant solution was cooled to 0 °C. To the solution was added 0.5 mL of TFA. After 5 minutes, a saturated aqueous NaHCO₃ solution was added and the separated aqueous layer was extracted with CHCl₃. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ("hexane/AcOEt = 8/2 to 5/5) to give the titled compound (96.6 mg, 2 steps, 50%) as a yellow amorphous; ¹H NMR (CDCl₃, δ) 7.38-7.35 (m, 4H), 7.30-7.28 (m, 2H), 7.11-7.04 (m, 3H), 6.94-6.90 (m, 2H), 6.56 (br, 2H), 4.83 (d, 1H, *J* = 14.9 Hz), 4.66 (d, 1H, *J* = 14.9 Hz), 3.68-3.59 (m, 3H), 3.41-3.39 (m, 1H), 2.88 (br, 1H), 2.55 (br, 1H); ¹³C NMR (CDCl₃, δ) 163.6, 147.3, 142.2, 137.2, 134.8, 132.6, 130.6, 128.5, 128.43, 128.39, 128.34, 128.1, 127.9, 127.4, 127.2, 125.9, 124.4, 117.5, 115.5, 50.0, 44.4, 29.7 ; IR (ATR) 3450, 2247, 1649 cm⁻¹; HRMS (MH⁺) calcd for C₂₄H₂₂³⁵ClN₂O: 389.1421. Found: 389.1421.



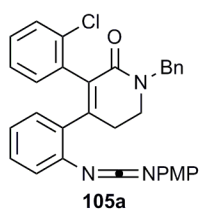
1-{2-[1-Benzyl-5-(2-chlorophenyl)-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]phenyl}-3-(4-methoxyphenyl)urea (104a) To a solution of diaryllactam **103** (335 mg, 861 μmol) in 5 mL of CH₂Cl₂ at ambient temperature, were added 4-methoxyphenyl isocyanate (123 μL, 947 μmol) and DMAP (10.0 mg, 81.9 μmol). The reaction mixture was stirred for 2 hours. 10 mL of Et₂O was added to the reaction mixture and a colorless precipitate was observed. The precipitate was collected by filtration, washed with CH₂Cl₂ and

dried in vacuo to give the titled compound (405 mg, 87%) as a colorless solid; mp 225-227 °C; ^1H NMR (DMSO- d_6 , δ) 8.91 (s, 1H), 7.88 (s, 1H), 7.73 (d, 1H, $J = 8.3$ Hz), 7.35-7.29 (m, 9H), 7.15-7.13 (m, 1H), 7.11-7.07 (m, 3H), 6.89-6.83 (m, 2H), 6.76 (d, 1H, $J = 3.4$ Hz), 4.95 (d, 1H, $J = 14.6$ Hz), 4.41 (d, 1H, $J = 14.6$ Hz), 3.72 (s, 3H), 3.55-3.54 (m, 2H), 3.00-2.91 (m, 1H), 2.49-2.37 (m, 2H); ^{13}C NMR (DMSO- d_6 , δ) 163.0, 154.5, 152.5, 147.3, 146.2, 137.5, 136.2, 135.4, 133.5, 132.6, 131.4, 130.9, 128.9, 128.5, 128.4, 128.0, 127.7, 127.3, 127.2, 126.5, 122.4, 121.7, 120.0, 114.1, 55.2, 49.5, 44.7, 29.0; IR (ATR) 3338, 1702, 1641 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{32}\text{H}_{29}^{35}\text{ClN}_3\text{O}_3$: 538.1897. Found: 538.1896.



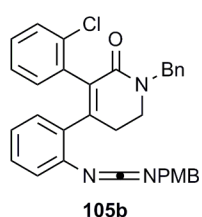
1-{2-[1-Benzyl-5-(2-chlorophenyl)-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]phenyl}-3-(4-methoxybenzyl)urea (104b) To a solution of diaryllactam **20** (93.0 mg, 239 μmol) in 1 mL of CH_2Cl_2 at ambient temperature, were added 4-methoxybenzyl isocyanate (40.5 μL , 263 μmol) and DMAP (9.6 mg, 78.6 μmol). The reaction mixture was heated to 40 °C and stirred for 24 hours. After cooled to ambient

temperature, the reaction mixture was directly subjected to silica gel column chromatography (n -hexane/AcOEt = 9/1 to 5/5) to give the titled compound (94.2 mg, 71%) as a colorless solid; mp 192-193 °C; ^1H NMR (CDCl_3 , δ) 7.79-7.65 (br, 1H), 7.31-7.06 (m, 12H), 6.82-6.78 (br, 3H), 6.65-6.55 (br, 2H), 6.35-6.16 (br, 1H), 5.58-4.62 (m, 1H), 4.24-4.19 (br, 2H), 4.01-3.98 (br, 1H), 3.76 (s, 3H), 3.62-3.59 (br, 1H), 3.24-2.91 (br, 2H), 2.38-2.27 (br, 1H); ^{13}C NMR (CDCl_3 , δ) 164.8, 158.5, 155.8, 148.4, 135.9, 135.7, 135.1, 133.5, 133.0, 132.0, 131.9, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.4, 126.2, 122.5, 113.8, 113.7, 55.2, 51.0, 45.4, 43.0, 29.0 (The peaks on ^1H and ^{13}C spectra were highly broadened.); IR (ATR) 3366, 1640 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{33}\text{H}_{31}^{35}\text{ClN}_3\text{O}_3$: 552.2054. Found: 552.2059.

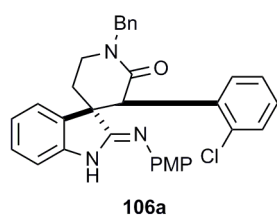


1-Benzyl-3-(2-chlorophenyl)-4-[2-(4-methoxyphenyliminomethyleneamino)phenyl]-5,6-dihydropyridin-2(1H)-one (105a) To a stirred solution of urea **104a** (404 mg, 751 μmol), PPh_3 (295 mg, 1.13 mmol), and Et_3N (230 μL , 1.65 mmol) in 10 mL of CH_2Cl_2 at 0 °C, was added CBr_4 (299 mg, 901 μmol). The reaction mixture was stirred for an hour and warmed to ambient temperature. Then additional PPh_3 (300 mg, 1.14

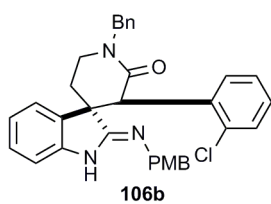
mmol) was added in three portions and the reaction mixture was stirred for 5 hours and directly evaporated. The resultant residue was purified by silica gel column chromatography (n -hexane/AcOEt = 8/2 to 7/3) to give the titled compound (379 mg, 97%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.40-7.38 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.27 (m, 2H), 7.13-7.00 (m, 7H), 6.94-6.84 (m, 4H), 4.83 (d, 1H, $J = 14.9$ Hz), 4.66 (d, 1H, $J = 14.9$ Hz), 3.79 (s, 3H), 3.68-3.66 (m, 1H), 3.48-3.43 (m, 1H), 3.07 (br, 1H), 2.60 (br, 1H); ^{13}C NMR (CDCl_3 , δ) 163.9, 157.5, 147.4, 137.5, 135.9, 135.6, 134.3, 134.2, 134.1, 132.4, 131.8, 130.3, 128.9, 128.8, 128.56, 128.55, 128.53, 128.2, 127.3, 126.1, 125.12, 125.05, 124.8, 114.8, 55.5, 50.3, 44.5, 30.2; IR (ATR) 2129, 1654 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{32}\text{H}_{27}^{35}\text{ClN}_3\text{O}_2$: 520.1792. Found: 520.1800.



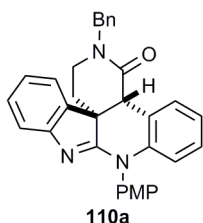
1-Benzyl-3-(2-chlorophenyl)-4-[2-(4-methoxybenzyl)iminomethyleneaminophenyl]-5,6-dihydropyridin-2(1H)-one (105b) To a stirred solution of urea **104b** (167 mg, 303 μmol), PPh_3 (119 mg, 454 μmol), and Et_3N (127 μL , 909 μmol) in 6 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added CBr_4 (121 mg, 364 μmol). The reaction mixture was stirred for an hour and warmed to ambient temperature. The reaction mixture was stirred for 10 hours and directly evaporated. The resultant residue was purified by silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 8/2$ to $6/4$) to give the titled compound (98.3 mg, 61%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.40-7.33 (m, 4H), 7.28-7.23 (m, 4H), 7.05-6.99 (m, 2H), 6.91-6.80 (m, 7H), 4.81 (d, 1H, $J = 14.6$ Hz), 4.65 (d, 1H, $J = 14.6$ Hz), 4.45 (s, 2H), 3.75 (s, 3H), 3.60-3.58 (m, 1H), 3.40-3.35 (m, 1H), 2.96 (s, 1H), 2.43-2.41 (m, 1H); ^{13}C NMR (CDCl_3 , δ) 163.9, 159.1, 147.8, 138.7, 137.5, 136.9, 135.8, 135.6, 134.1, 133.9, 131.9, 131.7, 129.8, 128.60, 128.57, 128.5, 128.4, 128.3, 128.2, 127.3, 126.0, 124.3, 124.0, 114.1, 55.2, 50.2, 49.9, 44.4, 29.9; IR (ATR) 2125, 1653 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{33}\text{H}_{29}^{35}\text{ClN}_3\text{O}_2$: 534.1948. Found: 534.1951.



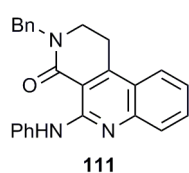
(3RS,3'RS,Z)-1'-Benzyl-3'-(2-chlorophenyl)-2-(4-methoxyphenylimino)spiro[indoline-3,4'-piperidin]-2'-one (106a) A solution of carbodiimide **105a** (354 mg, 681 μmol) and $t\text{BuOH}$ (651 μL , 6.81 mmol) in 12 mL of THF was degassed by freeze pump thaw cycles chilled with liquid nitrogen. To the stirred solution at ambient temperature, was added a solution of SmI_2 (0.1 M in THF, 19 mL, 1.90 mmol) in a dropwise manner over 4.5 hours. Then a saturated aqueous NH_4Cl solution was added to the reaction mixture and the organic solvent was removed by evaporation. The resultant mixture was extracted with AcOEt twice and the combined organic layers were washed with a saturated aqueous NH_4Cl solution and dried over Na_2SO_4 . The crude solution was concentrated under reduced pressure and dried in vacuo. The crude material was subjected to silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 8/2$ to $6/4$) to give the titled compound (307 mg, 86%) as a colorless solid; mp 208-209 $^\circ\text{C}$; ^1H NMR (CDCl_3 , δ) 7.50-7.32 (m, 6H), 7.19-7.13 (m, 3H), 6.94-6.92 (m, 1H), 6.87-6.68 (m, 5H), 6.59-6.53 (m, 3H), 5.03 (s, 1H), 4.97* (d, 1H, $J = 13.7$ Hz), 4.87 (d, 1H, $J = 14.3$ Hz), 4.83* (s, 1H), 4.76 (d, 1H, $J = 14.3$ Hz), 4.66* (d, 1H, $J = 13.7$ Hz), 3.88-3.82 (m, 1H), 3.79 (s, 3H), 3.77* (s, 3H), 3.64-3.62 (m, 1H), 2.58-2.52 (m, 1H), 2.22 (ddd, 1H, $J = 13.7, 5.7, 5.7$ Hz), 2.01-1.98* (m, 1H). ^{13}C NMR (CDCl_3 , δ) 169.9*, 169.1, 168.2*, 161.4, 156.1*, 155.7, 142.6, 142.2, 136.7, 136.4, 134.6, 134.4*, 133.9*, 132.4*, 132.3*, 130.3*, 130.0, 129.4, 129.3*, 129.2, 129.0*, 128.9*, 128.8, 128.7*, 128.6, 128.5, 128.3, 128.0*, 127.5, 126.1*, 125.9, 124.5, 123.0*, 122.1, 121.6*, 120.9, 118.1*, 114.7, 114.0*, 108.7, 56.8*, 55.4, 51.7, 51.3, 51.0*, 50.8, 49.5*, 43.9*, 43.2, 31.5*, 31.3; IR (ATR) 3246, 1667 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{32}\text{H}_{29}^{35}\text{ClN}_3\text{O}_2$: 522.1948. Found: 522.1946 (*peaks of minor isomer). Crystallographic data reported have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-927186. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U. K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).



(3*RS*,3'*RS*,*Z*)-1'-Benzyl-3'-(2-chlorophenyl)-2-(4-methoxybenzylimino)spiro[indoline-3,4'-piperidin]-2'-one (106b) A solution of carbodiimide **105b** (98.3 mg, 184 μ mol) and *t*BuOH (176 μ L, 1.84 mmol) in 1.8 mL of THF was degassed by freeze pump thaw cycles chilled with liquid nitrogen. To the stirred solution at ambient temperature, was added a solution of SmI₂ (0.9 M in THF/HMPA = 9/1, 8.18 mL) over 2 minutes. The reaction mixture was stirred for 5 minutes. Then a saturated aqueous NH₄Cl solution was added to the reaction mixture and the organic solvent was removed by evaporation. The resultant mixture was extracted with AcOEt twice and the combined organic layers were washed with a saturated aqueous LiCl solution twice and dried over Na₂SO₄. The crude solution was concentrated under reduced pressure. The crude material was subjected to silica gel column chromatography (ⁿhexane/AcOEt = 8/2 to 4/6) to give the titled compound (88.6 mg, 90%) as a colorless amorphous; ¹H NMR (CDCl₃, δ) 7.44-7.43 (m, 2H), 7.39-7.37 (m, 3H), 7.27-7.27 (m, 1H), 7.24-7.22 (m, 1H), 7.17-7.15 (m, 3H), 7.09-7.05 (m, 1H), 6.85-6.82 (m, 5H), 6.44 (d, 1H, *J* = 8.0 Hz), 4.93-4.89 (m, 2H), 4.64-4.62 (m, 2H), 4.54-4.50 (m, 1H), 4.35-4.32 (m, 1H), 3.81 (s, 3H), 3.77-3.74 (m, 1H), 3.59 (m, 1H), 2.36 (m, 1H), 1.94 (m, 1H); ¹³C NMR (CDCl₃, δ) 173.1, 168.1, 159.0, 155.9, 136.2, 134.5, 134.2, 130.1, 129.6, 129.5, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 127.9, 126.2, 123.0, 121.2, 117.3, 113.9, 55.6, 55.2, 50.8, 49.5, 46.4, 43.7, 31.9; IR (ATR) 3433, 1642cm⁻¹; HRMS (MH⁺) calcd for C₃₃H₃₁³⁵ClN₃O₂: 536.2105. Found: 536.2100.



(4a*RS*,14b*RS*)-2-Benzyl-10-(4-methoxyphenyl)-3,4,10,14b-tetrahydrobenzo[c]in do lo[3,2-j][2,6]naphthyridin-1(2*H*)-one (110a) A solution of iminoindoline **106a** (52.2 mg, 100 μ mol), NaO^{*t*}Bu (28.8 mg, 300 μ mol), Pd(OAc)₂ (2.1 mg, 5.09 μ mol), and Cy₃PH·BF₄ (3.7 mg, 10.0 μ mol) in 2 mL of DMA was heated at 120 °C for 17 hours. Then the reaction mixture was cooled to ambient temperature and a saturated aqueous NH₄Cl solution was added. The mixture was extracted with CHCl₃ three times and the combined organic layers were washed with H₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CHCl₃/AcOEt = 10/0 to 9/1) to give the titled compound (41.6 mg, 86%) as a colorless solid; mp 249-250 °C; ¹H NMR (CDCl₃, δ) 7.69 (d, 1H, *J* = 8.0 Hz), 7.39-7.34 (m, 7H), 7.19-7.08 (m, 6H), 6.85-6.81 (m, 2H), 6.57 (d, 1H, *J* = 8.0 Hz), 4.93 (d, 1H, *J* = 14.3 Hz), 4.74 (d, 1H, *J* = 14.3 Hz), 4.03 (s, 1H), 3.87 (s, 3H), 3.51 (ddd, 1H, *J* = 12.5, 7.0, 6.0 Hz), 3.30 (dd, 1H, *J* = 12.6, 7.0 Hz), 2.56 (ddd, 1H, *J* = 12.5, 7.0, 6.0 Hz), 1.42 (dd, 1H, *J* = 12.6, 6.0 Hz); ¹³C NMR (CDCl₃, δ) 171.8, 167.1, 159.4, 155.0, 140.6, 136.4, 136.1, 131.7, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 123.3, 122.3, 122.0, 120.0, 118.8, 117.0, 115.7, 115.5, 55.5, 50.4, 49.2, 45.6, 43.7, 24.8; IR (ATR) 1644, 1548 cm⁻¹; MS (MH⁺) calcd for C₃₂H₂₈N₃O₂: 486.2182. Found: 486.2182.

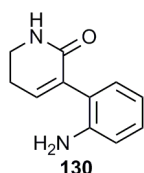


3-Benzyl-5-(phenylamino)-2,3-dihydrobenzo[c][2,7]naphthyridin-4(1*H*)-one (111) A solution of carbodiimide **75a** (60.8 mg, 160 μ mol) in 1.6 mL of THF was heated to 60 °C for 8 days. After cooled to ambient temperature, the reaction mixture was directly purified by preparative thin-layer chromatography (ⁿhexane/AcOEt = 7/3) to give the

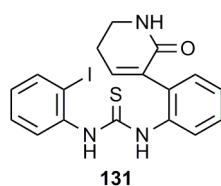
titled compound (35.8 mg, 59%) as a yellow crystal; mp. 166-168 °C; ¹H NMR (CDCl₃, δ) 11.52 (s, 1H), 8.00 (dd, 2H, *J* = 8.3, 1.0 Hz), 7.76 (d, 1H, *J* = 8.3 Hz), 7.67 (d, 1H, *J* = 8.3 Hz), 7.61-7.57 (m, 1H), 7.37-7.29 (m, 7H), 7.24-7.22 (m, 1H), 7.02 (t, 1H, *J* = 7.4 Hz), 4.79 (s, 2H), 3.55 (t, 2H, *J* = 7.0 Hz), 3.21 (t, 2H, *J* = 7.0 Hz); ¹³C NMR (CDCl₃, δ) 165.5, 152.4, 148.7, 147.5, 136.7, 131.5, 128.8, 128.6, 127.9, 127.7, 127.5, 123.7, 122.9, 121.9, 120.4, 120.0, 109.5, 50.3, 44.1, 23.8; IR (ATR) 3106, 3070, 1648, 1590, 1538, 1483, 1416 cm⁻¹; HRMS (MH⁺) calcd for C₂₅H₂₂N₃O: 380.1765. Found: 380.1764.



tert-Butyl [2-(2-Oxo-1,2,5,6-tetrahydropyridin-3-yl)phenyl]carbamate (129) A solution of boronic acid **98** (1.78 g, 7.50 mmol), lactam **128** (880 mg, 5.00 mmol), and PdCl₂(PPh₃)₂ (70.2 mg, 100 μmol) in 40 mL of dioxane and 40 mL of a 2.0 M aqueous Na₂CO₃ solution was heated to 100 °C for 30 minutes. The reaction mixture was cooled to ambient temperature and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/AcOEt = 3/7 to 1/9) to give the titled compound (1.27 g, 88%) as a gray solid; mp 156-160 °C; ¹H NMR (CDCl₃, δ) 7.84 (br, 1H), 7.75 (d, 1H, *J* = 8.5 Hz), 7.32 (ddd, 1H, *J* = 8.5, 7.2, 2.0 Hz), 7.10-7.04 (m, 2H), 6.67 (t, 1H, *J* = 4.4 Hz), 6.29 (br, 1H), 3.51 (td, 2H, *J* = 7.2, 4.6 Hz), 2.55 (m, 2H), 1.49 (s, 9H); ¹³C NMR (CDCl₃, δ) 166.6, 153.8, 142.0, 136.3, 135.2, 130.6, 129.7, 128.9, 123.9, 123.3, 79.7, 39.7, 28.3, 24.5; IR (ATR) 3016, 2981, 1709, 1668 cm⁻¹; HRMS (M⁺) calcd for C₁₆H₂₀N₂O₃: 288.1474. Found: 288.1472.

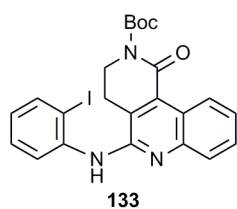


3-(2-Aminophenyl)-5,6-dihydropyridin-2(1H)-one (130) To a solution of lactam **129** (10.0 g, 34.7 mmol) in 315 mL of CH₂Cl₂ at 0 °C, was added 35 mL of TFA. After 20 minutes, the reaction mixture was warmed to ambient temperature and stirred for additional 3 hours. A saturated aqueous NaHCO₃ solution was added to the reaction mixture and the aqueous layer was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CHCl₃/MeOH = 95/5) to give the titled compound (6.46 g, 99%) as a gray solid; mp. 168-170 °C; ¹H NMR (CDCl₃, δ) 7.14 (ddd, 1H, *J* = 7.7, 7.7, 1.4 Hz), 7.02 (dd, 1H, *J* = 7.4, 1.4 Hz), 6.78 (ddd, 1H, *J* = 7.7, 7.7, 1.4 Hz), 6.72-6.69 (m, 2H), 5.94 (br, 1H), 4.00 (br, 2H), 3.53 (td, 2H, *J* = 7.2, 2.9 Hz), 2.56-2.52 (m, 2H); ¹³C NMR (CDCl₃, δ) 166.1, 145.0, 141.0, 135.4, 130.9, 129.1, 124.4, 118.9, 116.8, 39.8, 24.8; IR (ATR) 3225, 2919, 1665 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₃N₂O: 189.1028. Found: 189.1031.



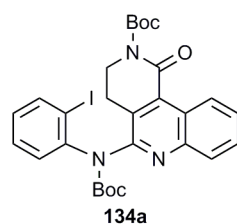
1-(2-Iodophenyl)-3-[2-(2-oxo-1,2,5,6-tetrahydropyridin-3-yl)phenyl]thiourea (131) A solution of aniline **130** (605 mg, 3.21 mmol), 2-iodophenyl isothiocyanate (1.84 mg, 7.06 mmol), and DMAP (58.9 mg, 0.482 mmol) in 32 mL of toluene was heated to 60 °C for 2 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. AcOEt was added to the residue and the resultant solid was filtered, washed with AcOEt, and dried in vacuo to give the titled compound (1.23 g, 85%) as a

colorless solid; mp. 178-180 °C; ^1H NMR (CDCl_3 , δ) 8.68 (br, 1H), 7.85 (d, 1H, $J = 8.3$ Hz), 7.76 (br, 1H), 7.68 (d, 1H, $J = 6.9$ Hz), 7.47-7.39 (m, 3H), 7.31-7.29 (m, 1H), 7.24-7.23 (m, 1H), 7.00 (dd, 1H, $J = 8.2$, 8.2 Hz), 6.78 (t, 1H, $J = 4.3$ Hz), 5.67 (br, 1H), 3.54-3.51 (m, 2H), 2.59-2.55 (m, 2H); ^{13}C NMR ($\text{DMSO}-d_6$, δ) 180.8, 165.2, 141.2, 140.7, 139.1, 137.2, 134.3, 133.8, 130.6, 129.8, 129.0, 128.9, 128.4, 127.7, 126.0, 100.0, 39.0, 24.4; IR (ATR) 3278, 3115, 2938, 1641, 1517 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$: 450.0137. Found: 450.0132.



***tert*-Butyl 5-[(2-Iodophenyl)amino]-1-oxo-3,4-dihydrobenzo[*c*][2,6]naphthyridine-2(1*H*)-carboxylate (133)**

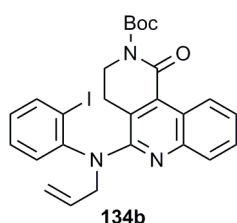
To a solution of thiourea **131** (5.00 g, 11.1 mmol) and Et_3N (6.19 mL, 44.4 mmol) in 800 mL of AcOEt at 0 °C, was added a solution of iodine (2.82 g, 11.1 mmol) in 200 mL of AcOEt in a dropwise manner over 20 minutes. After 1.5 hours, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude material. The solution of this crude material in 500 mL of DCE was heated at 80 °C for 9 hours. After cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. Et_2O was added to the residue, and the solution was extracted with a 3.0 M aqueous HCl solution twice. The combined aqueous layers were basified by solid Na_2CO_3 , and the solution was extracted with CHCl_3 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude material. The solution of this crude material, Boc_2O (2.40 g, 11.0 mmol), Et_3N (3.37 mL, 24.2 mmol) and DMAP (134 mg, 1.10 mmol) in 60 mL of THF was stirred at ambient temperature. After 1.5 hours, H_2O was added to the reaction mixture. The mixture was extracted with CHCl_3 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 9/1 to 8/2) to give the titled compound (3.92 g, 69%, 3 steps) as a yellow amorphus; ^1H NMR (CDCl_3 , δ) 8.93 (d, 1H, $J = 8.6$ Hz), 8.73 (d, 1H, $J = 8.0$ Hz), 7.87 (d, 1H, $J = 8.0$ Hz), 7.82 (dd, 1H, $J = 8.0$, 1.7 Hz), 7.62 (dd, 1H, $J = 8.0$, 1.7 Hz), 7.46-7.40 (m, 2H), 7.03 (br, 1H), 6.81 (ddd, 1H, $J = 8.0$, 8.0, 1.7 Hz), 4.11 (t, 2H, $J = 6.3$ Hz), 3.01 (t, 2H, $J = 6.3$ Hz), 1.63 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 162.6, 152.2, 150.0, 146.8, 140.1, 138.8, 133.6, 129.5, 129.2, 127.6, 126.2, 125.3, 124.4, 124.1, 121.5, 120.3, 90.2, 83.8, 43.0, 28.2, 24.3; IR (ATR) 3396, 2979, 1764, 1713, 1586 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3\text{I}$: 516.0784. Found: 516.0781.



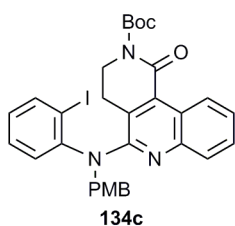
***tert*-Butyl 5-[(*tert*-Butoxycarbonyl)(2-iodophenyl)amino]-1-oxo-3,4-dihydrobenzo[*c*][2,6]naphthyridine-2(1*H*)-carboxylate (134a)**

To a solution of aminoquinoline **133** (155 mg, 301 μmol) in 2 mL of THF at ambient temperature, were added a solution of Boc_2O (78.8 mg, 361 μmol) in 1 mL of THF and DMAP (44.1 mg, 361 μmol). After 3 hours, a saturated aqueous NH_4Cl solution was added and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 100/0 to 95/5 to 85/15) to give the titled compound (171 mg, 92%) as a colorless

amorphus; ^1H NMR (CDCl_3 , δ) 9.00 (d, 1H, $J = 8.9$ Hz), 7.86-7.82 (m, 2H), 7.61-7.38 (m, 4H), 7.01 (dd, 1H, $J = 7.9$, 7.9 Hz), 4.04 (br, 2H), 3.26 (br, 2H), 1.62 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 162.8, 153.1, 151.9, 150.8, 150.8, 146.6, 143.9, 139.6, 134.3, 131.5, 129.3, 129.0, 128.7, 128.6, 128.0, 125.7, 123.8, 98.9, 83.6, 82.4, 43.7, 28.03, 28.00, 26.2; IR (ATR) 2978, 1767, 1713 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{28}\text{H}_{31}\text{N}_3\text{O}_5$: 616.1308. Found: 616.1307.



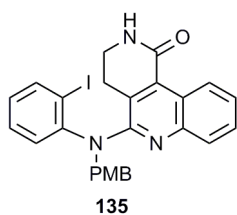
tert-Butyl 5-[Allyl(2-iodophenyl)amino]-1-oxo-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (134b) To a solution of aminoquinoline **133** (155 mg, 301 μmol) in 2.4 mL of THF at 0 $^\circ\text{C}$ were added allyl iodide (33.0 μL , 361 μmol) and a suspension of NaH (60% wt, 12.0 mg, 301 μmol) in 0.6 mL of DMF. After 4 hours, a saturated aqueous NH_4Cl solution was added to the reaction mixture. The mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (n hexane/AcOEt = 9/1 to 8/2) to give the titled compound (139 mg, 83%) as an orange amorphus; ^1H NMR (CDCl_3 , δ) 8.85 (d, 1H, $J = 8.0$ Hz), 7.98 (d, 1H, $J = 8.0$ Hz), 7.92 (d, 1H, $J = 7.7$ Hz), 7.63 (dd, 1H, $J = 7.7$, 7.7 Hz), 7.45 (dd, 1H, $J = 8.0$, 8.0 Hz), 7.21 (dd, 1H, $J = 8.0$, 8.0 Hz), 6.93 (dd, 1H, $J = 7.7$, 7.7 Hz), 6.68 (d, 1H, $J = 7.7$ Hz), 6.34-6.26 (m, 1H), 5.18 (d, 1H, $J = 17.2$ Hz), 5.10 (d, 1H, $J = 10.0$ Hz), 4.52 (d, 2H, $J = 6.3$ Hz), 3.76 (br, 2H), 2.12 (br, 2H), 1.56 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 163.0, 155.1, 151.7, 148.8, 146.7, 140.8, 134.6, 134.5, 129.4, 129.2, 128.9, 128.04, 128.00, 127.6, 125.7, 125.6, 122.0, 118.3, 99.5, 83.5, 55.0, 43.7, 28.0, 25.8; IR (ATR) 2979, 1717, 1699 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{26}\text{H}_{27}\text{IN}_3\text{O}_3$: 556.1097. Found: 556.1099.



tert-Butyl 5-[(2-Iodophenyl)(4-methoxybenzyl)amino]-1-oxo-3,4-dihydrobenzo[c][2,6] naphthyridine-2(1H)-carboxylate (134c) To a solution of aminoquinoline **133** (515 mg, 1.00 mmol) in 4 mL of THF at 0 $^\circ\text{C}$, were added *p*-methoxybenzyl iodide (322 mg, 1.30 mmol)* and a suspension of NaH (60% wt, 44.0 mg, 1.10 mmol) in 2 mL of DMF. After 20 minutes, a saturated aqueous NaHCO_3 solution was added to the reaction mixture. The aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/AcOEt = 9/1 to 8/2) to give the titled compound (581 mg, 91%) as an orange amorphus; ^1H NMR (CDCl_3 , δ) 8.82 (d, 1H, $J = 8.3$ Hz), 7.99 (d, 1H, $J = 8.0$ Hz), 7.90 (d, 1H, $J = 8.3$ Hz), 7.62 (dd, 1H, $J = 7.6$, 7.6 Hz), 7.47-7.42 (m, 3H), 7.12 (dd, 1H, $J = 7.6$, 7.6 Hz), 6.92 (dd, 1H, $J = 7.6$, 7.6 Hz), 6.72 (d, 2H, $J = 8.6$ Hz), 6.50 (d, 1H, $J = 8.0$ Hz), 5.13 (s, 2H), 3.80-3.74 (m, 2H), 3.72 (s, 3H), 2.23-2.15 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 163.0, 158.4, 155.2, 151.8, 148.6, 146.6, 140.9, 134.7, 130.7, 130.1, 129.4, 129.1, 128.1, 128.0, 127.68, 127.67, 125.7, 125.6, 122.0, 113.1, 99.1, 83.5, 55.0, 54.4, 43.7, 28.0, 25.9; IR (ATR) 2977, 1715, 1300, 1147 cm^{-1} ; HRMS (M^+) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_3\text{O}_4\text{I}$: 635.1281. Found: 635.1271.

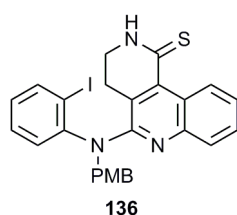
* *p*-Methoxybenzyl iodide was prepared by the reported procedure (F. Bilodeau, L. Dubé; P.

Deslongchamps, *Tetrahedron* **2003**, *59*, 2781.).



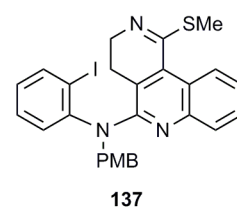
5-[(2-Iodophenyl)(4-methoxybenzyl)amino]-3,4-dihydrobenzo[c][2,6]naphthyridin-1(2H)-one (135)

To a solution of aminoquinoline **134a** (3.00 g, 4.72 mmol) in 180 mL of CH₂Cl₂ at 0 °C was added 20 mL of TFA. After 20 minutes, a saturated aqueous NaHCO₃ solution was added to the reaction mixture. The aqueous layer was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (ⁿhexane/AcOEt = 6/4 to 5/5) to give the titled compound (2.50 g, 99%) as an orange amorphus; ¹H NMR (CDCl₃, δ) 9.00 (d, 1H, *J* = 8.3 Hz), 7.98 (d, 1H, *J* = 7.6 Hz), 7.88 (d, 1H, *J* = 8.3 Hz), 7.61 (dd, 1H, *J* = 7.0, 7.0 Hz), 7.50 (d, 2H, *J* = 8.6 Hz), 7.44 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.12 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.90 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.73 (d, 2H, *J* = 8.6 Hz), 6.53 (d, 1H, *J* = 7.6 Hz), 6.14 (s, 1H), 5.10 (s, 2H), 3.72 (s, 3H), 3.32 (td, 2H, *J* = 6.4, 3.7 Hz), 2.26-2.19 (m, 2H); ¹³C NMR (CDCl₃, δ) 166.0, 158.3, 155.4, 149.1, 146.4, 140.8, 133.6, 130.55, 130.47, 129.3, 129.1, 129.0, 128.0, 127.9, 127.4, 125.9, 125.4, 122.1, 113.1, 99.0, 55.0, 54.7, 39.2, 25.9; IR (ATR) 3206, 3061, 1667, 1466, 1244 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₂₃N₃O₂I: 536.0829. Found: 536.0838.



5-[(2-Iodophenyl)(4-methoxybenzyl)amino]-3,4-dihydrobenzo[c][2,6]naphthyridin-1(2H)-thione (136)

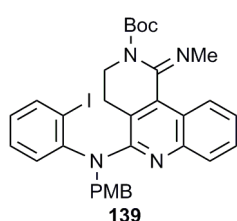
A solution of aminoquinoline **135** (425 mg, 794 μmol) and Lawesson's reagent (177 mg, 437 μmol) in 12 mL of toluene was heated to 100 °C for 1 hour. After the reaction mixture was cooled to ambient temperature, a saturated aqueous NaHCO₃ solution was added. The aqueous layer was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (toluene/ⁿhexane/AcOEt = 10/0/0 to 5/5/0 to 0/10/0 to 0/6/4) to give the titled compound (424 mg, 97%) as a yellow amorphus; ¹H NMR (CDCl₃, δ) 9.30 (d, 1H, *J* = 8.3 Hz), 8.56 (s, 1H), 7.96 (d, 1H, *J* = 6.6 Hz), 7.88 (d, 1H, *J* = 7.2 Hz), 7.60 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.47 (d, 2H, *J* = 8.6 Hz), 7.42 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.11 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.89 (d, 1H, *J* = 7.6, 7.6 Hz), 6.71 (d, 2H, *J* = 8.6 Hz), 6.58 (d, 1H, *J* = 8.0 Hz), 5.12 (s, 2H), 3.72 (s, 3H), 3.25 (dd, 2H, *J* = 11.0, 6.2 Hz), 2.21-2.15 (m, 2H); ¹³C NMR (CDCl₃, δ) 191.5, 158.4, 155.1, 148.8, 146.9, 140.8, 138.7, 130.7, 130.3, 129.5, 129.4, 129.1, 128.0, 127.6, 126.3, 124.6, 122.3, 122.1, 113.1, 99.1, 55.1, 54.5, 41.2, 26.3; IR (ATR) 3170, 1508, 1321, 1174 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₂₃N₃O₂S: 552.0601. Found: 552.0598.



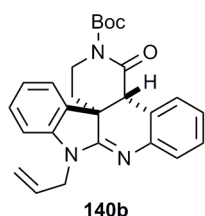
N-(2-Iodophenyl)-N-(4-methoxybenzyl)-1-(methylthio)-3,4-dihydrobenzo[c][2,6]naphthyridin-5-amine (137)

A solution of thiolactam **136** (405 mg, 734 μmol), K₂CO₃ (710 mg, 5.14 mmol), and MeI (274 μL, 4.40 mmol) in 9 mL of THF was stirred at ambient temperature for 44 hours. H₂O was added to the reaction mixture and the aqueous layer was extracted with AcOEt twice. The combined organic

layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (ⁿhexane/AcOEt = 9/1 to 8/2) to give the titled compound (371 mg, 89%) as a pale yellow amorphus; ¹H NMR (CDCl₃, δ) 8.71 (d, 1H, *J* = 8.3 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.3 Hz), 7.60 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.45 (d, 2H, *J* = 8.6 Hz), 7.38 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.11 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.88 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.71 (d, 2H, *J* = 8.6 Hz), 6.59 (d, 1H, *J* = 8.0 Hz), 5.16 (s, 2H), 3.71 (s, 3H), 3.47-3.41 (m, 2H), 2.47 (s, 3H), 1.87-1.81 (m, 2H); ¹³C NMR (CDCl₃, δ) 163.7, 158.3, 155.6, 148.7, 146.6, 140.7, 135.6, 130.7, 130.4, 129.4, 129.3, 128.8, 128.3, 127.4, 126.2, 124.9, 124.0, 120.2, 113.0, 99.2, 55.0, 54.3, 48.0, 24.3, 13.8; IR (ATR) 2925, 1547, 1244, 1173 cm⁻¹; HRMS (MH⁺) calcd for C₂₇H₂₅N₃O₃I: 566.0758. Found: 566.0748.

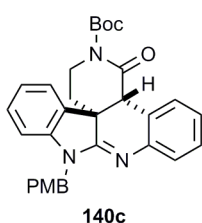


tert-Butyl 5-[(2-Iodophenyl)(4-methoxybenzyl)amino]-1-(methylimino)-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (139) A solution of methyl thioimidate **137** (1.44 g, 2.55 mmol) in 25 mL of a 2.0 M methylamine solution in MeOH was heated to 80 °C in a sealed tube for 47 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a crude material. A solution of this crude material, Boc₂O (557 mg, 2.55 mmol), and Et₃N (782 μL, 5.61 mmol) in 35 mL of THF was stirred at ambient temperature for 17 hours. To the reaction mixture was added brine and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ⁿhexane/AcOEt = 9/1 to 8/2) to give the titled compound (1.44 g, 2 steps, 87%) as a pale yellow amorphus; ¹H NMR (CDCl₃, δ) 8.48 (d, 1H, *J* = 8.3 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 7.86 (d, 1H, *J* = 8.3 Hz), 7.58 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.52 (d, 2H, *J* = 8.6 Hz), 7.39 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.10 (dd, 1H, *J* = 7.7, 7.7 Hz), 6.87 (dd, 1H, *J* = 7.7, 7.7 Hz), 6.72 (d, 2H, *J* = 8.6 Hz), 6.61 (d, 1H, *J* = 8.0 Hz), 5.06 (s, 2H), 3.71 (s, 3H), 3.54-3.49 (m, 2H), 3.37 (s, 3H), 2.35-2.20 (m, 2H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, δ) 158.2, 155.2, 151.8, 149.9, 148.1, 146.4, 145.1, 140.9, 140.8, 130.8, 130.4, 129.3, 128.9, 127.9, 127.3, 125.3, 125.1, 124.5, 121.3, 113.1, 99.0, 81.6, 55.1, 55.0, 44.4, 39.5, 28.2, 23.8; IR (ATR) 2981, 1715, 1318 cm⁻¹; HRMS (MH⁺) calcd for C₃₂H₃₄N₄O₃I: 649.1670. Found: 649.1677.



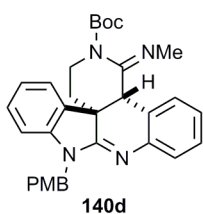
tert-Butyl (4aRS,14bRS)-9-Allyl-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (140b) To a solution of lactam **134b** (55.5 mg, 99.9 μmol) in 2 mL of THF at -78 °C was added ⁿBuLi (1.60 M in ⁿhexane, 68.7 μL, 110 μmol) in a dropwise manner over 5 minutes. After 20 minutes, the reaction mixture was warmed to 0 °C and stirred for additional 30 minutes. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution and the aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (ⁿhexane/AcOEt = 9/1 to 8/2) to give the titled compound (29.3 mg, 68%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.32-7.25 (m, 4H), 7.21 (d, 1H, *J* = 7.2 Hz), 7.09 (dd, 1H, *J* = 7.4, 7.4 Hz), 7.00 (dd, 1H, *J* = 7.4, 7.4 Hz), 6.87 (d, 1H, *J* = 8.0

H₂), 5.96-5.91 (m, 1H), 5.28-5.19 (m, 2H), 4.71 (dd, 1H, *J* = 16.6, 5.2 Hz), 4.36 (dd, 1H, *J* = 16.6, 5.2 Hz), 3.95 (s, 1H), 3.71-3.65 (m, 2H), 2.42-2.33 (m, 1H), 1.60 (s, 9H), 1.42-1.40 (m, 1H); ¹³C NMR (CDCl₃, δ) 170.0, 166.4, 153.3, 144.9, 144.0, 131.5, 130.6, 129.1, 129.0, 126.4, 125.4, 124.6, 123.6, 121.4, 120.0, 117.4, 109.1, 83.5, 49.3, 43.5, 43.5, 43.4, 42.6, 28.0, 25.3; IR (ATR) 2979, 1716, 1643 cm⁻¹; HRMS (MH⁺) calcd for C₂₆H₂₈N₃O₃: 430.2130. Found: 430.2130.



tert-Butyl (4aR,14bR)-9-(4-Methoxybenzyl)-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (140c) To a solution of lactam **134c** (63.5 mg, 99.9 μmol) in 2 mL of THF at -78 °C was added ⁿBuLi (1.58 M in ⁿhexane, 68.7 μL, 110 μmol) in a dropwise manner over 5 minutes. After 20 minutes, the reaction mixture was warmed to 0 °C and stirred for additional 30 minutes. The

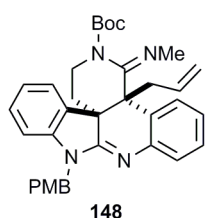
reaction mixture was quenched with a saturated aqueous NH₄Cl solution and the aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (ⁿhexane/AcOEt = 95/5 to 85/15) to give the titled compound (34.5 mg, 68%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.35-7.19 (m, 7H), 7.10 (dd, 1H, *J* = 7.2, 7.2 Hz), 6.96 (dd, 1H, *J* = 7.7, 7.7 Hz), 6.85 (d, 2H, *J* = 8.3 Hz), 6.76 (d, 1H, *J* = 7.7 Hz), 5.26 (d, 1H, *J* = 15.8 Hz), 4.85 (d, 1H, *J* = 15.8 Hz), 3.99 (s, 1H), 3.76 (s, 3H), 3.71-3.67 (m, 2H), 2.44-2.41 (m, 1H), 1.60 (s, 9H), 1.45-1.42 (m, 1H); ¹³C NMR (CDCl₃, δ) 170.0, 166.7, 159.0, 153.3, 144.8, 144.1, 130.5, 129.1, 129.0, 128.5, 128.1, 126.4, 125.5, 124.6, 123.5, 121.3, 120.0, 114.1, 109.1, 83.5, 55.2, 49.3, 44.1, 43.6, 42.6, 28.0, 25.3; IR (ATR) 2975, 1716, 1645 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₃₂N₃O₄: 510.2393. Found: 510.2398.



tert-Butyl (4aRS,14bRS)-9-(4-Methoxybenzyl)-1-(methylimino)-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (140d) To a solution of aminoquinoline **139** (97.3 mg, 150 μmol) in 3 mL of THF at -78 °C was added ⁿBuLi (1.58 M in ⁿhexane, 199 μL, 315 μmol) in a dropwise manner over 5 minutes. After 20 minutes, the reaction mixture was warmed to 0 °C and stirred for additional

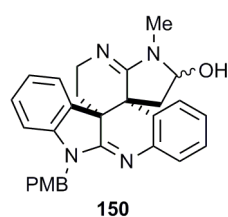
30 minutes. A saturated aqueous NaHCO₃ solution was added to the reaction mixture and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography (ⁿhexane/AcOEt = 9/1 to 8/2) to give the titled compound (57.7 mg, 74%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.45 (d, 1H, *J* = 7.6 Hz), 7.32-7.23 (m, 4H), 7.18 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.08 (d, 1H, *J* = 7.4 Hz), 7.03 (dd, 1H, *J* = 7.2, 7.2 Hz), 6.91 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.73 (d, 1H, *J* = 8.0 Hz), 5.27 (d, 1H, *J* = 15.8 Hz), 4.86 (d, 1H, *J* = 15.8 Hz), 4.33-4.22 (m, 1H), 4.04 (s, 1H), 3.76 (s, 3H), 3.38 (s, 3H), 3.29-3.18 (m, 1H), 2.33-2.27 (m, 1H), 1.57 (s, 9H), 1.24-1.18 (m, 1H); ¹³C NMR (CDCl₃, δ) 167.5, 158.9, 152.2, 144.8, 144.5, 131.7, 128.64, 128.62, 128.57, 128.45, 128.3, 128.1, 125.0, 124.3, 123.7, 120.8, 121.6, 114.1, 109.0, 82.0, 55.2, 50.1, 45.7, 44.0, 40.4, 39.4, 28.4, 27.6; IR (ATR) 2977, 2870, 1704, 1591, 1352, 1135 cm⁻¹; HRMS (M⁺) calcd for C₃₂H₃₄N₄O₃: 522.2631. Found: 522.2637.

Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-945651. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, U. K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).



***tert*-Butyl (4a*SR*,14b*RS*)-14b-Allyl-9-(4-methoxybenzyl)-1-(methylimino)-1,3,4,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridine-2(9*H*)-carboxylate (148)**

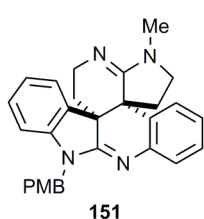
To a solution of aminoquinoline **139** (97.2 mg, 150 μmol) in 3 mL of THF at $-78\text{ }^\circ\text{C}$ was added $n\text{BuLi}$ (1.58 M in $n\text{hexane}$, 199 μL , 315 μmol) in a dropwise manner over 5 minutes. After 20 minutes, the reaction mixture was warmed to $0\text{ }^\circ\text{C}$ and stirred for additional 15 minutes and allyl iodide (29.0 μL , 315 μmol) was added. After additional 20 minutes, a saturated aqueous NaHCO_3 solution was added to the reaction mixture and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography ($n\text{hexane}/\text{ether} = 7/3$ to $6/4$) to give the titled compound (56.6 mg, 67%) as a colorless amorphus; ^1H NMR (CDCl_3 , δ) 7.34 (d, 2H, $J = 8.3$ Hz), 7.27 (d, 1H, $J = 7.7$ Hz), 7.24-7.20 (m, 2H), 7.17 (dd, 1H, $J = 7.7, 7.7$ Hz), 7.01-6.98 (m, 2H), 6.90 (dd, 1H, $J = 7.4, 7.4$ Hz), 6.85 (d, 2H, $J = 8.6$ Hz), 6.72 (d, 1H, $J = 7.7$ Hz), 5.48-5.39 (m, 1H), 5.32 (d, 1H, $J = 15.6$ Hz), 4.65 (d, 1H, $J = 15.6$ Hz), 4.50 (d, 1H, $J = 10.3$ Hz), 4.30-4.17(m, 2H), 3.77 (s, 3H), 3.38 (s, 3H), 3.22 (dd, 1H, $J = 13.5, 11.2$ Hz), 2.54 (dd, 1H, $J = 13.9, 3.3$ Hz), 2.44-2.38 (m, 1H), 2.29 (dd, 1H, $J = 13.9, 10.2$ Hz), 1.54 (s, 9H), 1.33-1.27 (m, 1H); ^{13}C NMR (CDCl_3 , δ) 168.3, 158.9, 154.7, 152.0, 145.3, 144.7, 134.8, 129.8, 128.7, 128.5, 128.44, 128.41, 128.37, 125.0, 124.9, 124.3, 123.5, 120.7, 117.0, 114.0, 108.9, 81.6, 55.2, 53.0, 50.9, 44.1, 40.6, 39.3, 31.5, 28.4, 28.1; IR (ATR) 2981, 1702, 1645, 1590, 1464, 1367, 1250 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{35}\text{H}_{39}\text{N}_4\text{O}_3$: 563.3017. Found: 563.3021.



(3a*RS*,13b*SR*)-9-(4-Methoxybenzyl)-1-methyl-1,2,3,9,14,15-hexahydrobenzo[*c*]indolo[3,2-*j*]pyrrolo[3,2-*e*][2,6]naphthyridin-2-ol (150)

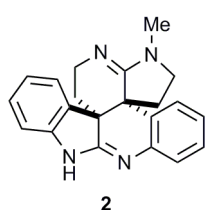
To a solution of allyl pentacyclic bisamidine **148** (136 mg, 242 μmol) and NMO (113 mg, 968 μmol) in 3.5 mL of acetone at ambient temperature, was added an OsO_4 solution (20 mg/mL in H_2O , 615 μL , 48.4 μmol). After 1.5 hours, a saturated aqueous Na_2SO_3 solution was added to the reaction mixture and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude material. To a solution of the crude material and NaHCO_3 (81.3 mg, 968 μmol) in 2 mL of THF and 2 mL of H_2O at ambient temperature, was added NaIO_4 (207 mg, 968 μmol). After 16 hours, a saturated aqueous NaHCO_3 solution was added to the reaction mixture and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography ($\text{AcOEt}/\text{MeOH} = 10/0$ to $9/1$) to give the titled compound (83.5 mg, 75%, 2 steps) as a colorless amorphus, diastereomeric mixture (dr = 3:2); ^1H NMR (CDCl_3 , δ) 7.29-7.26 (m, 1.6H), 7.24-7.18 (m, 2.6H), 7.15-7.09 (m, 1.4H), 7.00-6.93 (m, 1.6H),

6.88-6.78 (m, 3.8H), 6.70-6.67 (m, 1H), 5.10-4.98 (m, 2.4H), 4.84 (d, 0.6H, $J = 6.6$ Hz), 3.75 (s, 2H), 3.74 (s, 1H), 3.61-3.56 (m, 2H), 3.14 (s, 2H), 3.09 (s, 1H), 2.26-2.13 (m, 2.4H), 1.87 (m, 1H), 1.59 (dd, 0.6H, $J = 12.5, 6.4$ Hz), 1.36-1.30 (m, 1H); ^{13}C NMR (CDCl_3 , δ) 168.0, 167.9, 161.4, 160.5, 158.9, 158.8, 145.1, 143.7, 143.4, 130.8, 129.4, 129.3, 128.7, 128.62, 128.56, 128.46, 128.43, 128.3, 128.20, 128.18, 125.23, 125.16, 124.9, 124.4, 124.3, 124.2, 124.0, 121.8, 121.7, 114.0, 109.0, 84.8, 82.5, 55.2, 46.1, 46.0, 44.4, 43.90, 43.86, 42.9, 42.7, 39.9, 39.0, 29.2, 27.3, 25.4, 25.1; IR (ATR) 3060, 2932, 1637, 1584, 1465 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{29}\text{H}_{29}\text{N}_4\text{O}_2$: 465.2285. Found: 465.2281.



(3aRS,13bSR)-9-(4-Methoxybenzyl)-1-methyl-1,2,3,9,14,15-hexahydrobenzo[c]indolo[3,2-j]pyrrolo[3,2-e][2,6]naphthyridine (151) To a solution of hemiaminal **150** (25.4 mg, 54.7 μmol , diastereomeric mixture) in 0.7 mL of MeOH at 0 $^\circ\text{C}$, were added a NaCNBH_3 solution (1.0 M in THF, 54.7 μL , 54.7 μmol) and AcOH (31.3 μL , 547 μmol). After 20 minutes the reaction mixture was warmed to 60 $^\circ\text{C}$ and stirred for

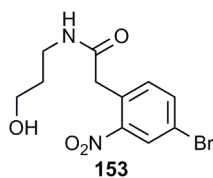
additional 15 hours. After the reaction mixture was cooled to ambient temperature, a saturated aqueous NaHCO_3 solution was added to the reaction mixture. The mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 4/6$ to $3/7$) to give the titled compound (18.5 mg, 76%) as a colorless amorphus; ^1H NMR (CDCl_3 , δ) 7.28 (d, 2H, $J = 8.6$ Hz), 7.25-7.21 (m, 2H), 7.14 (dd, 1H, $J = 7.7, 7.7$ Hz), 7.08 (d, 1H, $J = 7.2$ Hz), 7.00-6.96 (m, 1H), 6.91-6.86 (m, 2H), 6.83 (d, 2H, $J = 8.3$ Hz), 6.69 (d, 1H, $J = 8.0$ Hz), 5.12 (d, 1H, $J = 15.6$ Hz), 5.00 (d, 1H, $J = 15.6$ Hz), 3.76 (s, 3H), 3.70-3.57 (m, 2H), 3.36-3.30 (m, 1H), 3.15 (s, 3H), 3.06 (dd, 1H, $J = 9.0, 9.0$ Hz), 2.28-2.18 (m, 1H), 1.90-1.84 (m, 1H), 1.69 (dd, 1H, $J = 11.7, 5.7$ Hz), 1.30 (dd, 1H, $J = 13.3, 6.2$ Hz); ^{13}C NMR (CDCl_3 , δ) 168.1, 161.3, 158.9, 145.2, 143.5, 129.2, 128.6, 128.50, 128.48, 128.45, 128.3, 125.2, 125.1, 124.5, 124.1, 121.5, 114.1, 108.8, 55.2, 46.7, 46.5, 46.1, 43.9, 43.0, 31.0, 29.8, 25.0; IR (ATR) 2982, 2869, 1645, 1589 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{29}\text{H}_{29}\text{N}_4\text{O}$: 449.2336. Found: 449.2342.



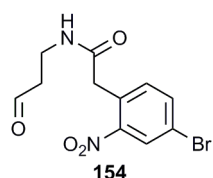
Dehaloperophoramidine (2) To a solution of hexacyclic bisamidine **151** (18.5 mg, 41.2 μmol) in 1.8 mL of anisole was added 0.2 mL of H_3PO_4 . The reaction mixture was heated to 120 $^\circ\text{C}$ and stirred for 48 hours. The reaction mixture was cooled to ambient temperature and 1.8 mL of H_2O was added. $^n\text{Hexane}$ was added to the mixture and after vigorous stirring the organic layer was removed. This washing was repeated

additionally twice. The aqueous layer was basified with a 2.0 M aqueous NaOH solution and extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 1/9$ to $0/10$) to give dehaloperophoramidine **2** (9.6 mg, 71%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.29-7.23 (m, 2H), 7.18 (d, 1H, $J = 7.7$ Hz), 7.14-7.10 (m, 2H), 7.00 (dd, 1H, $J = 7.0, 7.0$ Hz), 6.97 (dd, 1H, $J = 7.0, 7.0$ Hz), 6.93 (d, 1H, $J = 7.4$ Hz), 3.72-3.69 (2H, m), 3.32 (ddd, 1H, $J = 9.6, 9.6, 5.7$ Hz), 3.15 (s, 3H), 3.06 (dd, 1H, $J = 9.0, 9.0$ Hz), 2.26 (ddd, 1H, $J = 13.2, 8.9, 8.9$ Hz), 1.88-1.82 (m, 1H), 1.74 (dd, 1H, $J = 12.0,$

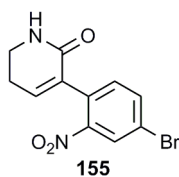
6.0 Hz), 1.35 (ddd, 1H, $J = 13.2, 5.0, 2.4$ Hz); ^{13}C NMR (CDCl_3 , δ) 172.5, 160.9, 150.8, 138.8, 132.5, 128.7, 128.4, 127.3, 126.0, 124.0, 123.6, 122.0, 119.8, 114.1, 50.1, 46.6, 46.0, 43.2, 31.0, 29.9, 25.3; IR (ATR) 3384, 2982, 1650 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_4$: 329.1761. Found: 329.1761.



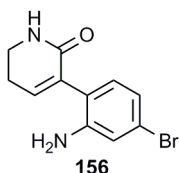
2-(4-Bromo-2-nitrophenyl)-*N*-(3-hydroxypropyl)acetamide (153) To a solution of carboxylic acid (7.80 g, 30.0 mmol) and HOBt monohydrate (4.69 g, 30.6 mmol) in 150 mL of CH_2Cl_2 at 0 °C, was added a solution of DCC (6.31 g, 30.6 mmol) in 25 mL of CH_2Cl_2 over 5 minutes. After the reaction mixture was stirred for 20 minutes, 3-aminopropan-1-ol (2.75 mL, 36.0 mmol) was added over 3 minutes. After 15 minutes, the reaction mixture was warmed to ambient temperature and stirred for 19 hours. The resultant suspension was filtered through a pad of Celite[®] and the filtrate was washed with a saturated aqueous NaHCO_3 solution. The separated aqueous layer was extracted with CHCl_3 and the combined organic layers were washed with a saturated aqueous NaHCO_3 solution, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ($\text{CHCl}_3/\text{MeOH} = 100/0$ to 95/5 to 90/10) to give the titled compound (8.11 g, 85%) as a colorless solid; mp. 118-120 °C; ^1H NMR (CDCl_3 , δ) 8.20 (d, 1H, $J = 2.0$ Hz), 7.73 (dd, 1H, $J = 8.0, 2.0$ Hz), 7.37 (d, 1H, $J = 8.0$ Hz), 6.17 (s, 1H), 3.81 (s, 2H), 3.63 (s, 2H), 3.44-3.43 (m, 2H), 1.71-1.67 (m, 2H); ^{13}C NMR (CDCl_3 , δ) 169.5, 149.1, 136.6, 134.8, 129.3, 128.0, 121.6, 59.5, 40.4, 36.8, 32.0; IR (ATR) 3566, 3289, 1640, 1560, 1514, 1347 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4^{79}\text{Br}$: 317.0137. Found: 317.0135.



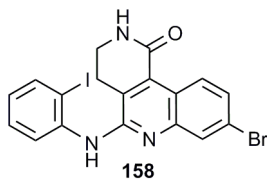
2-(4-Bromo-2-nitrophenyl)-*N*-(3-oxopropyl)acetamide (154) To a solution of oxalyl chloride (6.43 mL, 75.0 mmol) in 500 mL of CH_2Cl_2 at -78 °C, was added DMSO (10.6 mL, 150 mmol) over 5min. After the solution was stirred for 5 minutes, a suspension of alcohol **153** (7.93 g, 25.0 mmol) in 150 mL of CH_2Cl_2 was added over 10 minutes and the resultant suspension was stirred for 5 minutes. After addition of Et_3N (27.9 mL, 200 mmol), the suspension was warmed to 0 °C over an hour and stirred for additional 10 minutes at the same temperature. A saturated aqueous NH_4Cl solution was added and the separated aqueous layer was extracted with CHCl_3 . The combined organic layers were washed with H_2O three times and dried over Na_2SO_4 . Evaporation of the organic layer and drying under reduced pressure gave the titled compound (7.84 g, 99%) in an analytically pure form as a colorless solid; mp. 114-116 °C; ^1H NMR (CDCl_3 , δ) 9.80 (s, 1H), 8.19 (d, 1H, $J = 2.0$ Hz), 7.72 (dd, 1H, $J = 8.3, 2.0$ Hz), 7.31 (d, 1H, $J = 8.3$ Hz), 6.28 (s, 1H), 3.77 (s, 2H), 3.54 (q, 2H, $J = 5.7$ Hz), 2.75 (t, 2H, $J = 5.7$ Hz); ^{13}C NMR (CDCl_3 , δ) 201.5, 168.4, 149.2, 136.5, 134.7, 129.2, 128.1, 121.6, 43.5, 40.5, 33.2; IR (ATR) 3288, 1713, 1639, 1522, 1349 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4^{79}\text{Br}$: 314.9980. Found: 314.9975.



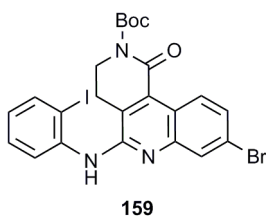
3-(4-Bromo-2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (155) To a solution of aldehyde **154** (39.0 g, 124 mmol) in 900 mL of THF at 0 °C, was added DBU (25.9 mL, 173 mmol) over 5 minutes in a dropwise manner. After 30 minutes, the reaction mixture was warmed to ambient temperature and stirred for 5 hours. A saturated aqueous NH₄Cl solution was added and the aqueous layer was extracted with THF. The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated under reduced pressure, and dried by toluene azeotropy. The crude material and Et₃N (51.8 mL, 372 mmol) was dissolved in 600 mL of CH₂Cl₂ and MsCl (19.2 mL, 248 mmol) was added to the solution over 30 minutes. After 20 minutes, a saturated aqueous NH₄Cl solution was added and the organic layer was washed with H₂O twice. The resultant solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was dissolved in 600 mL of MeOH. To the mixture at 0 °C, was added NaO^tBu (8.56 g, 89.1 mmol) in several portions and the reaction mixture was stirred for 20 minutes. Then the precipitate was collected by filtration. The filtrate was concentrated under reduced pressure to 100 mL and the resultant precipitation was collected by filtration. The combined precipitate was washed with H₂O twice and drying under reduced pressure gave the titled compound (29.3 g, 80%, 3 steps) as a colorless solid; mp. 205 °C (decomp.); ¹H NMR (DMSO-*d*₆, δ) 8.15 (d, 1H, *J* = 2.0 Hz), 7.93 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.74 (s, 1H), 7.42 (d, 1H, *J* = 8.3 Hz), 6.92 (t, 1H, *J* = 4.3 Hz), 3.33-3.32 (m, 2H), 2.45-2.43 (m, 2H); ¹³C NMR (DMSO-*d*₆, δ) 163.1, 148.9, 138.9, 136.2, 133.3, 132.8, 131.1, 126.4, 120.7, 38.7, 24.0; IR (ATR) 3187, 1664, 1526, 1350 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₀N₂O₃⁸¹Br: 298.9855. Found: 298.9854.



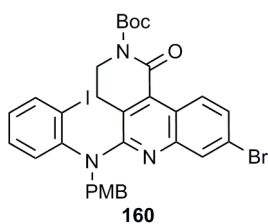
3-(2-Amino-4-bromophenyl)-5,6-dihydropyridin-2(1H)-one (156) A suspension of lactam **155** (297 mg, 1.00 mmol), NH₄Cl (348 mg, 6.50 mmol) and powdered iron (335 mg, 6.00 mmol) in 8 mL of MeOH and 4 mL of H₂O was heated to reflux for 2 hours. The resultant hot solution was filtrated through a pad of Celite[®] and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and dissolved in CHCl₃. The solution was extracted with a 6.0 M aqueous HCl solution twice and the combined organic layers were neutralized using solid NaHCO₃. The aqueous layer was extracted with CHCl₃ three times and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CHCl₃/MeOH = 100/0 to 95/5) to give the titled compound (230 mg, 86%) as a colorless solid; mp. 170 °C (decomp.); ¹H NMR (DMSO-*d*₆, δ) 7.58 (s, 1H), 6.81 (s, 1H), 6.73 (d, 1H, *J* = 8.0 Hz), 6.63 (d, 1H, *J* = 8.0 Hz), 6.57 (t, 1H, *J* = 3.9 Hz), 5.00 (s, 2H), 3.34-3.31 (m, 2H), 2.38-2.36 (m, 2H); ¹³C NMR (DMSO-*d*₆, δ) 164.5, 148.2, 140.8, 133.2, 132.3, 122.1, 120.9, 118.0, 116.7, 38.7, 24.2; IR (ATR) 3313, 1673, 1619, 1415 cm⁻¹; HRMS (MH⁺) calcd for C₁₁H₁₂N₂O⁷⁹Br: 267.0133. Found: 276.0126.



8-Bromo-5-((2-iodophenyl)amino)-3,4-dihydrobenzo[c][2,6]naphthyridin-1(2H)-one (158) A solution of aniline **156** (1.34 g, 5.02 mmol), 2-iodophenyl isothiocyanate (2.61 g, 10.0 mmol), and DMAP (91.6 mg, 750 μmol) in 50 mL of DCE was heated to 60 $^{\circ}\text{C}$ for 7 hours. After cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure. 30 mL of Et_2O was added to the crude material and, after ultrasonication, the precipitate was collected by filtration and washed with 30 mL of Et_2O twice. Drying of the precipitate under reduced pressure gave a colorless solid (2.64 g). To a suspension of the solid and Et_3N (2.79 mL, 20.0 mmol) in 100 mL of AcOEt at 0 $^{\circ}\text{C}$, was added a solution of iodine (1.27 g, 5.00 mmol) in 30 mL of AcOEt over 5 minutes. After 15 minutes, the reaction mixture was filtrated using a piece of filter paper and the solvent of the filtrated was substituted with 150 mL of DCE by evaporation. Then the resultant solution was heated to 80 $^{\circ}\text{C}$ for 6 hours. After cooled to ambient temperature, the reaction mixture was evaporated and Et_2O was added. The suspension was extracted with a HCl 6.0 M aqueous solution twice and the combined aqueous layers were neutralized with solid NaHCO_3 . The aqueous layer was extracted CHCl_3 three times and the combined organic layer was dried over Na_2SO_4 , concentrated under reduced pressure. The crude material was washed with mixture of CHCl_3 and AcOEt (1:1) and drying of the resultant solid gave the titled compound (1.72 g, 3 steps, 69%) as a pale yellow solid; mp. 241-242 $^{\circ}\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, δ) 8.94 (d, 1H, $J = 9.2$ Hz), 8.45 (s, 1H), 8.38 (s, 1H), 7.92 (d, 1H, $J = 8.0$ Hz), 7.80 (dd, 1H, $J = 8.0, 1.4$ Hz), 7.63 (d, 1H, $J = 1.4$ Hz), 7.45-7.42 (m, 2H), 6.99 (t, 1H, $J = 7.6$ Hz), 3.48-3.46 (m, 2H), 2.97 (t, 2H, $J = 6.6$ Hz); ^{13}C NMR ($\text{DMSO}-d_6$, δ) 163.7, 152.8, 147.2, 141.5, 138.9, 132.1, 128.8, 128.2, 126.8, 126.7, 126.0, 125.2, 121.9, 119.6, 97.9, 37.7, 23.5; IR (ATR) 3393, 3187, 3095, 1677, 1580, 1523, 1488, 1430 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}^{79}\text{BrI}$: 493.9365. Found: 493.9362.

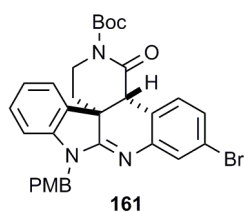


tert-Butyl 8-Bromo-5-((2-iodophenyl)amino)-1-oxo-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (159) To a suspension of aminoquinoline **158** (3.38 g, 6.84 mmol) in 30 mL of THF at 0 $^{\circ}\text{C}$, were added a solution of Boc_2O (1.49 g, 6.84 mmol) in 5 mL of THF and solid DMAP (83.6 mg, 684 μmol). After 5 minutes, the reaction mixture was warmed to ambient temperature and stirred for an hour. A saturated aqueous NH_4Cl solution was added and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and the crude material was purified by silica gel column chromatography (n hexane/AcOEt = 95/5 to 85/15) to give the titled compound (3.77 g, 93%) as a yellow solid; mp. 241-242 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , δ) 8.81 (d, 1H, $J = 9.2$ Hz), 8.76 (dd, 1H, $J = 8.3, 1.4$ Hz), 8.02 (d, 1H, $J = 2.0$ Hz), 7.83-7.81 (m, 1H), 7.48 (dd, 1H, $J = 9.2, 2.0$ Hz), 7.44-7.41 (m, 1H), 7.07 (s, 1H), 6.83 (td, 1H, $J = 7.6, 1.4$ Hz), 4.12 (t, 2H, $J = 6.2$ Hz), 3.02 (t, 2H, $J = 6.2$ Hz), 1.62 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 162.3, 152.0, 147.7, 139.6, 138.8, 133.3, 129.7, 129.2, 128.4, 127.7, 124.6, 124.5, 123.7, 120.6, 120.1, 90.4, 84.0, 42.7, 28.1, 24.1; IR (ATR) 3396, 1756, 1586, 1524, 1434 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3^{79}\text{BrI}$: 593.9889. Found: 593.9883.

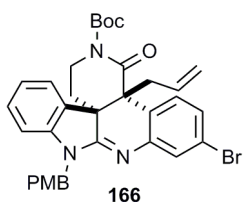


tert-Butyl 8-Bromo-5-((2-iodophenyl)(4-methoxybenzyl)amino)-1-oxo-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (160) To a solution of aminoquinoline **159** (7.21 g, 12.1 mmol) in 60 mL of THF at 0 °C, were added *p*-methoxybenzyl iodide (3.84 g, 15.5 mmol)* and a suspension of NaH (60% wt, 532 mg, 13.3 mmol) in 30 mL of DMF. After 20 minutes, a saturated aqueous NaHCO₃ solution was added to the reaction mixture. The aqueous layer was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ⁿhexane/AcOEt = 100/0 to 85/15) to give the titled compound (8.07 g, 93%) as an orange amorphus; ¹H NMR (CDCl₃, δ) 8.71 (d, 1H, *J* = 9.0 Hz), 8.06 (d, 1H, *J* = 2.1 Hz), 7.98 (d, 1H, *J* = 7.6 Hz), 7.50 (dd, 1H, *J* = 9.0, 2.1 Hz), 7.40 (d, 2H, *J* = 8.6 Hz), 7.13 (t, 1H, *J* = 7.6 Hz), 6.93 (t, 1H, *J* = 7.6 Hz), 6.73 (d, 2H, *J* = 8.6 Hz), 6.49 (dd, 1H, *J* = 7.6, 1.6 Hz), 5.12 (br s, 2H), 3.77-3.75 (m, 5H), 2.13 (br s, 2H), 1.55 (s, 9H); ¹³C NMR (CDCl₃, δ) 162.8, 158.5, 155.9, 151.6, 148.1, 147.4, 141.0, 134.8, 130.8, 130.0, 129.8, 129.6, 129.5, 128.7, 128.2, 128.0, 127.3, 123.4, 120.7, 113.2, 99.1, 83.8, 55.1, 54.3, 43.6, 28.0, 26.0; IR (ATR) 1713, 1444, 1408, 1300 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₃₀N₃O₄⁸¹BrI: 714.0444. Found: 714.0444.

* *p*-Methoxybenzyl iodide was prepared by the reported procedure (Bilodeau, F.; Dubé, L.; Deslongchamps, P. *Tetrahedron* **2003**, *59*, 2781.).

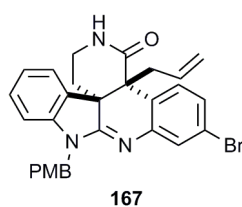


tert-Butyl (4aRS,14bRS)-12-Bromo-9-(4-methoxybenzyl)-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (161) To a solution of aminoquinoline **160** (3.40 g, 4.76 mmol) in 50 mL of THF at -78 °C was added ⁿBuLi (1.64 M in ⁿhexane, 3.19 mL, 5.24 mmol) in a dropwise manner over 5 minutes. After an hour, the reaction mixture was quenched with a saturated aqueous NH₄Cl solution and the aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ⁿhexane/AcOEt = 100/ to 85/15) to give the titled compound (2.52 g, 90%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.44 (d, 1H, *J* = 1.4 Hz), 7.29 (d, 2H, *J* = 8.6 Hz), 7.26-7.19 (m, 4H), 6.98 (t, 1H, *J* = 7.4 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 6.80 (d, 1H, *J* = 8.0 Hz), 5.23 (d, 1H, *J* = 15.8 Hz), 4.84 (d, 1H, *J* = 15.8 Hz), 3.90 (s, 1H), 3.77 (s, 3H), 3.69-3.68 (m, 2H), 2.40-2.37 (m, 1H), 1.59 (s, 9H), 1.43-1.41 (m, 1H); ¹³C NMR (CDCl₃, δ) 169.5, 167.5, 159.0, 153.2, 145.9, 144.6, 130.4, 129.2, 128.6, 128.2, 127.9, 127.8, 127.2, 123.5, 122.5, 121.7, 118.9, 114.2, 109.3, 83.7, 55.2, 48.7, 44.2, 43.6, 42.6, 28.0, 25.4; IR (ATR) 2976, 2931, 1768, 1717, 1643, 1607, 1576, 1461, 1288, 1246, 1143 cm⁻¹; HRMS (MH⁺) calcd for C₃₁H₃₁N₃O₄⁷⁹Br: 588.1498. Found: 588.1505.



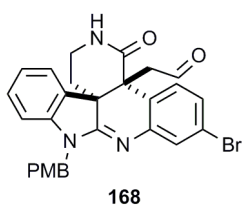
tert-Butyl (4aSR,14bRS)-14b-Allyl-12-bromo-9-(4-methoxybenzyl)-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (166) To a solution of lactam **161** (177 mg, 301 μmol) in 1.5 mL of THF at -78 °C, was added KHMDS (1.0 M in THF, 452 μL, 452 μmol). After a minute, allyl iodide

(36.0 μL , 391 μmol) was added and immediately the reaction mixture was warmed to ambient temperature and stirred for 10 minutes. A saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ("hexane/ AcOEt = 9/1 to 8/2) to give the titled compound (183 mg, 97%) as a colorless amorphus; ^1H NMR (CDCl_3 , δ) 7.41 (d, 1H, J = 2.0 Hz), 7.35 (d, 2H, J = 8.6 Hz), 7.24-7.12 (m, 5H), 6.98 (t, 1H, J = 7.4 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.79 (d, 1H, J = 8.0 Hz), 5.39-5.30 (m, 1H), 5.24 (d, 1H, J = 15.5 Hz), 4.68 (d, 1H, J = 15.5 Hz), 4.47 (d, 1H, J = 9.6 Hz), 4.17 (d, 1H, J = 16.9 Hz), 3.78 (s, 3H), 3.75-3.63 (m, 2H), 2.68 (dd, 1H, J = 14.2, 5.2 Hz), 2.52-2.49 (m, 1H), 2.24 (dd, 1H, J = 14.2, 9.6 Hz), 1.57 (s, 9H), 1.46 (m, 1H); ^{13}C NMR (CDCl_3 , δ) 172.8, 168.4, 159.0, 153.5, 145.9, 145.0, 133.4, 129.0, 128.9, 128.5, 128.1, 128.0, 127.1, 125.2, 124.1, 123.1, 122.3, 121.4, 117.8, 114.0, 109.2, 83.3, 55.1, 52.8, 48.4, 44.3, 42.4, 28.8, 27.9; IR (ATR) 2977, 2932, 1768, 1717, 1642, 1606, 1574, 1462, 1247, 1147 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{34}\text{H}_{35}\text{N}_3\text{O}_4^{81}\text{Br}$: 630.1791. Found: 630.1782.



(4aSR,14bRS)-14b-Allyl-12-bromo-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-1(2H)-one (167) To a solution of lactam **166** (44.4 mg, 70.6 μmol) in 0.9 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 0.1 mL of TFA. After 10 minutes, a saturated aqueous NaHCO_3 solution was added and the resultant mixture was extracted with CHCl_3 twice. The combined organic layers

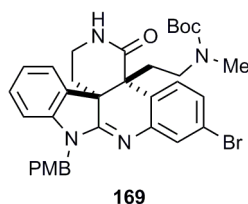
were dried over Na_2SO_4 and concentration and drying under reduced pressure gave the titled product (36.2 mg, 97%) as a colorless amorphus; ^1H NMR (CDCl_3 , δ) 7.50 (d, 1H, J = 8.3 Hz), 7.39 (d, 1H, J = 2.3 Hz), 7.36 (d, 2H, J = 8.6 Hz), 7.27 (d, 1H, J = 7.7 Hz), 7.23 (t, 1H, J = 7.7 Hz), 7.16 (dd, 1H, J = 8.3, 2.3 Hz), 6.97 (t, 1H, J = 7.7 Hz), 6.87 (d, 2H, J = 8.6 Hz), 6.80 (d, 1H, J = 7.7 Hz), 6.65 (br s, 1H), 5.34-5.28 (m, 2H), 4.66 (d, 1H, J = 15.5 Hz), 4.44 (d, 1H, J = 10.0 Hz), 4.14 (d, 1H, J = 16.9 Hz), 3.78 (s, 3H), 3.54-3.52 (m, 1H), 3.33-3.29 (m, 1H), 2.80 (dd, 1H, J = 13.7, 5.2 Hz), 2.50 (td, 1H, J = 13.0, 6.3 Hz), 2.29 (dd, 1H, J = 14.2, 9.6 Hz), 1.40 (dd, 1H, J = 13.7, 5.2 Hz); ^{13}C NMR (CDCl_3 , δ) 172.2, 168.5, 159.0, 146.1, 145.2, 133.7, 129.0, 128.9, 128.2, 128.13, 128.12, 127.9, 127.0, 124.5, 123.9, 122.1, 121.3, 117.6, 114.0, 109.1, 55.2, 49.7, 47.2, 44.3, 40.4, 38.2, 27.2; IR (ATR) 3200, 1642, 1605, 1572, 1512, 1457, 1368, 1246, cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_2^{81}\text{Br}$: 530.1266. Found: 530.1263.



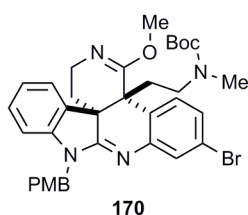
2-((4aSR,14bRS)-12-Bromo-9-(4-methoxybenzyl)-1-oxo-1,2,3,4,9,14b-hexahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-14b-yl)acetaldehyde (168) To a solution of lactam **167** (550 mg, 1.04 mmol) and NMO (488 mg, 4.16 mmol) in 10 mL of acetone at ambient temperature, was added an OsO_4 solution (20 mg/mL in H_2O , 1.32 mL, 104 μmol). After 1.5 hours, a saturated aqueous Na_2SO_3 solution

was added to the reaction mixture and the resultant mixture was extracted with CHCl_3 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To a solution of the crude material in 9 mL of THF and 1 mL of H_2O at ambient temperature, was added NaIO_4 (1.33 g, 6.24 mmol).

After 3.5 hours, a saturated aqueous NaHCO₃ solution was added to the reaction mixture and the resultant mixture was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CHCl₃/MeOH = 10/0 to 96/4) to give the titled compound (546 mg, 99%, 2 steps) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 9.53 (d, 1H, *J* = 4.3 Hz), 7.45 (d, 1H, *J* = 2.0 Hz), 7.35 (d, 1H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.6 Hz), 7.22-7.20 (m, 3H), 7.03 (br s, 1H), 6.97 (t, 1H, *J* = 7.6 Hz), 6.86 (d, 2H, *J* = 8.6 Hz), 6.81 (d, 1H, *J* = 7.6 Hz), 5.16 (d, 1H, *J* = 15.8 Hz), 4.92 (d, 1H, *J* = 15.8 Hz), 3.77 (s, 3H), 3.57-3.54 (m, 1H), 3.39-3.37 (m, 1H), 2.56 (td, 1H, *J* = 13.0, 6.7 Hz), 2.45 (dd, 1H, *J* = 15.8, 4.3 Hz), 2.16 (d, 1H, *J* = 15.8 Hz), 1.46 (dd, 1H, *J* = 13.7, 5.2 Hz); ¹³C NMR (CDCl₃, δ) 199.2, 171.4, 167.3, 159.0, 145.2, 144.8, 129.5, 128.6, 128.3, 127.7, 127.2, 124.1, 123.1, 123.0, 122.0, 114.2, 109.6, 55.2, 48.7, 47.9, 44.2, 43.5, 38.1, 24.4; IR (ATR) 3249, 1713, 1639, 1605, 1573, 1512, 1457, 1369 cm⁻¹; HRMS (MH⁺) calcd for C₂₈H₂₅N₃O₃⁷⁹Br: 530.1079. Found: 530.1086.

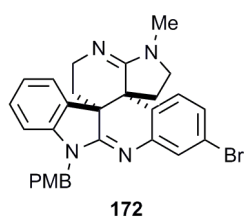


tert-Butyl (2-((4aSR,14bRS)-12-Bromo-9-(4-methoxybenzyl)-1-oxo-1,2,3,4,9,14b-hexahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-14b-yl)ethyl)(methyl)carbamate (169) A solution of aldehyde **168** (485 mg, 914 μmol), MeNH₃Cl (309 mg, 4.57 mmol), and NaOAc (600 mg, 7.31 mmol) in 10 mL of MeOH was stirred at ambient temperature for 12 hours. The reaction mixture was cooled to 0 °C and NaBH₄ (450 mg, 9.14 mmol) was added at once. After 10 minutes, a saturated aqueous NaHCO₃ solution was added and the resultant mixture was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentration under reduced pressure. To a solution of the crude material in 5 mL of THF at 0 °C, were added Boc₂O (399 mg, 1.83 mmol) and Et₃N (191 μL, 1.37 mmol). After 5 minutes, the reaction mixture was warmed to ambient temperature and stirred for 2.5 hours. Then the reaction mixture was directly evaporated and purified by NH silica gel column chromatography (ⁿhexane/AcOEt = 5/5) to give the titled compound (446 mg, 76%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.39 (br s, 1H), 7.35-7.33 (m, 3H), 7.25-7.24 (m, 3H), 7.16 (br d, 1H, *J* = 10.0 Hz), 6.98 (br t, 1H, *J* = 7.2 Hz), 6.86-6.84 (m, 3H), 6.03 (br s, 1H), 5.22 (br d, 1H, *J* = 15.8 Hz), 4.85 (br d, 1H, *J* = 15.8 Hz), 3.76 (s, 3H), 3.51 (td, 1H, *J* = 12.3, 5.3 Hz), 3.29-3.23 (m, 2H), 2.53-2.41 (m, 5H), 1.94 (td, 1H, *J* = 12.7, 4.6 Hz), 1.63-1.57 (m, 2H), 1.34-1.26 (m, 11H); ¹³C NMR (CDCl₃, δ) 172.3, 167.8, 159.1, 155.2, 145.6, 144.6, 129.2, 129.1, 128.9, 128.3, 128.1, 127.8, 126.9, 124.2, 123.4, 122.2, 121.6, 114.1, 109.4, 78.9, 55.2, 48.2, 47.9, 46.2, 44.1, 38.1, 33.6, 31.7, 28.1, 26.2; IR (ATR) 3212, 1664, 1644, 1576, 1463, 1367 cm⁻¹; HRMS (MH⁺) calcd for C₃₄H₃₈N₄O₄⁸¹Br: 647.2056. Found: 647.2062.



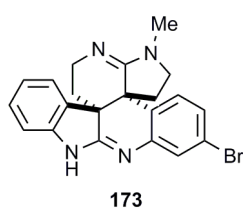
tert-Butyl (2-((4aSR,14bRS)-12-Bromo-1-methoxy-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-14b-yl)ethyl)(methyl)carbamate (170) To a suspension of lactam **169** (115 mg, 178 μmol) and NaHCO₃ (44.9 mg, 534 μmol) in 1.8 mL of CH₂Cl₂ at ambient temperature, was added Me₃O·BF₄ (71.0 mg, 480 μmol) in three portions over 6 hours. After additional 3

hours, a saturated aqueous NaHCO₃ solution was added and the resultant mixture was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel preparative thin-layer chromatography (CHCl₃/MeOH = 97/3) to give the titled compound (63.3 mg, 54%) as a colorless oil; ¹H NMR (CDCl₃, δ) 7.35-7.34 (m, 3H), 7.20 (br t, 2H, *J* = 7.9 Hz), 7.12 (br d, 1H, *J* = 7.7 Hz), 7.05 (br d, 1H, *J* = 7.4 Hz), 6.94 (br t, 1H, *J* = 7.4 Hz), 6.85-6.83 (m, 3H), 5.20-4.86 (m, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.63-3.59 (m, 2H), 3.13-3.10 (s, 1H), 2.35-2.27 (m, 5H), 1.87-1.84 (m, 1H), 1.60-1.58 (br s, 1H), 1.39-1.13 (m, 10H); ¹³C NMR (CDCl₃, δ) 168.7, 142.2, 159.1, 155.2, 145.8, 144.5, 128.9, 128.8, 128.73, 128.68, 128.1, 121.5, 114.1, 109.2, 78.9, 55.2, 52.9, 47.9, 46.6, 44.9, 44.1, 42.1, 33.6, 31.6, 28.2, 27.0; IR (ATR) 2975, 2940, 1692, 1573, 1644, 1576, 1513, 1464, 1367, 1249 cm⁻¹; HRMS (MH⁺) calcd for C₃₅H₄₀N₄O₄⁸¹Br: 661.2212. Found: 661.2217.



(3aRS,13bSR)-6-Bromo-9-(4-methoxybenzyl)-1-methyl-1,2,3,9,14,15-hexahydrobenzo[c]indolo[3,2-j]pyrrolo[3,2-e][2,6]naphthyridine (172) To a solution of methyl imidate **170** (110 mg, 167 μmol) in 7.2 mL of CH₂Cl₂ at 0 °C, was added 0.8 mL of TFA. After an hour, the reaction mixture was warmed to ambient temperature and stirred for 8 hours. Then a saturated aqueous NaHCO₃ solution was added and

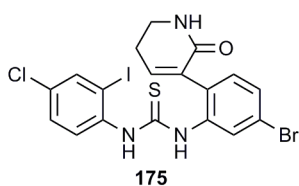
the resultant mixture was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. A solution of the crude material in 10 mL of toluene was heated to 100 °C for 24 hours. After cooled to ambient temperature, the reaction mixture was evaporated and direct NH silica gel column chromatography (AcOEt) gave the titled product (71.7 mg, 2 steps, 81%) as a colorless crystal; mp. 215 °C (decomp.); ¹H NMR (CDCl₃, δ) 7.38 (d, 1H, *J* = 2.0 Hz), 7.27 (d, 2H, *J* = 8.6 Hz), 7.16 (td, 1H, *J* = 7.7, 1.1 Hz), 7.08 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.06 (dd, 1H, *J* = 7.4, 1.1 Hz), 6.91 (td, 1H, *J* = 7.4, 1.1 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 6.73 (d, 2H, *J* = 8.0 Hz), 5.10 (d, 1H, *J* = 15.5 Hz), 4.98 (d, 1H, *J* = 15.5 Hz), 3.77 (s, 3H), 3.68 (dd, 1H, *J* = 17.2, 7.4 Hz), 3.63-3.56 (m, 1H), 3.29 (td, 1H, *J* = 9.7, 5.7 Hz), 3.12 (s, 3H), 3.05 (t, 1H, *J* = 8.9 Hz), 2.21-2.17 (m, 1H), 1.85-1.82 (m, 1H), 1.64 (dd, 1H, *J* = 11.7, 5.4 Hz), 1.29 (dd, 1H, *J* = 13.5, 5.4 Hz); ¹³C NMR (CDCl₃, δ) 168.9, 160.7, 159.0, 145.5, 144.9, 129.1, 128.6, 128.5, 128.2, 128.1, 127.6, 126.5, 126.4, 124.5, 121.8, 121.6, 114.1, 109.0, 55.2, 46.6, 45.7, 44.0, 42.9, 31.0, 29.7, 25.0; IR (ATR) 2945, 1663, 1634, 1604, 1572, 1455, 1371 cm⁻¹; HRMS (MH⁺) calcd for C₂₉H₂₈N₄O⁷⁹Br: 527.1446. Found: 527.1453.



(3aRS,13bSR)-6-Bromo-1-methyl-1,2,3,9,14,15-hexahydrobenzo[c]indolo[3,2-j]pyrrolo[3,2-e][2,6]naphthyridine (173) To a solution of bisamidine **172** (35.8 mg, 67.9 μmol) in 2.7 mL of anisole at ambient temperature, was added 0.3 mL of H₃PO₄. The reaction mixture was heated to 120 °C and stirred for 48 hours. The reaction mixture was cooled to ambient temperature and 2.7 mL of H₂O was added.

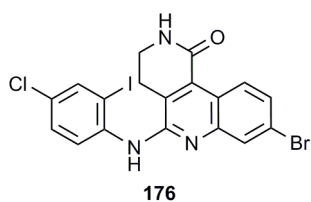
Hexane was added to the mixture and after vigorous stirring the organic layer was removed. This washing was repeated additionally three times. The aqueous layer was basified with a 2.0 M aqueous NaOH solution

and extracted with AcOEt twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by NH silica gel column chromatography (AcOEt) to give the titled compound (23.9 mg, 86%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.32 (d, 1H, *J* = 2.0 Hz), 7.29 (td, 1H, *J* = 7.6, 1.1 Hz), 7.15-7.10 (m, 3H), 6.98 (t, 1H, *J* = 7.4 Hz), 6.79 (d, 1H, *J* = 8.3 Hz), 3.77-3.64 (m, 2H), 3.30 (td, 1H, *J* = 9.8, 4.9 Hz), 3.14 (s, 3H), 3.07 (t, 1H, *J* = 9.0 Hz), 2.23-2.20 (m, 1H), 1.87-1.84 (m, 1H), 1.72 (dd, 1H, *J* = 12.0, 5.7 Hz), 1.36 (ddd, 1H, *J* = 13.4, 5.9, 1.4 Hz); ¹³C NMR (CDCl₃, δ) 172.6, 160.3, 148.5, 141.7, 131.3, 128.9, 127.3, 126.6, 126.3, 124.2, 123.8, 122.1, 121.6, 113.0, 49.2, 46.5, 45.5, 43.0, 31.0, 29.7, 25.1; IR (ATR) 3117, 2886, 2855, 1665, 1647, 1579, 1467 cm⁻¹; HRMS (MH⁺) calcd for C₂₁H₂₀N₄⁷⁹Br: 407.0871. Found: 407.0865.



1-(5-Bromo-2-(2-oxo-1,2,5,6-tetrahydropyridin-3-yl)phenyl)-3-(4-chloro-2-iodophenyl)thiourea (175) A solution of aniline **156** (399 mg, 1.49 mmol), 4-chloro-2-iodophenyl isothiocyanate (463 mg, 1.57 mmol), and DMAP (27.3 mg, 224 μmol) in 3 mL of DCE was heated to 60 °C for 3 hours. After cooled to ambient temperature, the reaction mixture was concentrated under reduced

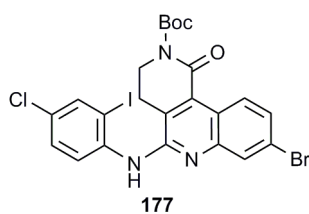
pressure. To the resultant solid was added Et₂O and, after ultrasonication, the precipitation was collected by filtration. The precipitate was washed with Et₂O and dried under reduced pressure to give the titled compound (832 mg, 99%) as an off-white solid; mp. 146-147 °C; ¹H NMR (DMSO-*d*₆, δ) 9.74 (s, 1H), 9.26 (s, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.72 (br s, 1H), 7.47 (d, 1H, *J* = 8.6 Hz), 7.39-7.36 (m, 2H), 7.13 (d, 1H, *J* = 8.3 Hz), 6.71 (t, 1H, *J* = 4.2 Hz), 3.32 (t, 2H, *J* = 6.7 Hz), 2.43-2.42 (m, 2H); ¹³C NMR (DMSO-*d*₆, δ) 180.8, 164.7, 141.7, 138.6, 137.7, 133.2, 132.4, 132.3, 131.9, 130.7, 128.8, 128.5, 119.6, 100.8, 79.2, 38.7, 24.2; IR (ATR) 3196, 3186, 3095, 1676, 1580, 1569, 1514, 1487, 1401, 1328 cm⁻¹; HRMS (MH⁺) calcd for C₁₈H₁₅N₃OBrClI: 561.8852. Found: 561.8843.



8-Bromo-5-((4-chloro-2-iodophenyl)amino)-3,4-dihydrobenzo[c][2,6]naphthyridin-1(2H)-one (176) To a suspension of thiourea **175** (225 mg, 400 μmol) and Et₃N (223 μL, 1.60 mmol) in 2 mL of DCE at 0 °C, was added a solution of iodine (117 mg, 461 μmol) in 10 mL of DCE over 5 minutes. After 5 minutes, a saturated aqueous Na₂S₂O₃ solution was added and the organic

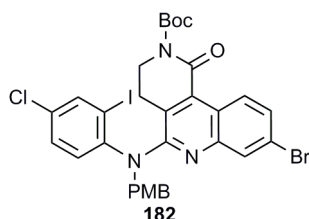
layer was washed with H₂O. The combined aqueous layer was extracted with DCE and the combined organic layers were washed with brine and dried over Na₂SO₄. The resultant solution was concentrated under reduced pressure to 30 mL and heated to 80 °C for 8.5 hours. After cooled to ambient temperature, the reaction mixture was concentrated under reduced pressure to 1.5 mL and kept at 0 °C for 12 hours. The precipitate was collected by filtration and washed with 1 mL of DCE to give the titled compound (139 mg, 2 steps, 66%) as a yellow solid; mp. 270-272 °C; ¹H NMR (DMSO-*d*₆, δ) 8.88 (d, 1H, *J* = 8.6 Hz), 8.41-8.40 (m, 2H), 7.93 (d, 1H, *J* = 2.3 Hz), 7.72 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.59 (s, 1H), 7.46 (dd, 1H, *J* = 8.6, 2.3 Hz), 7.39-7.37 (m, 1H), 3.41-3.39 (m, 2H), 2.91 (t, 2H, *J* = 6.3 Hz); ¹³C NMR (DMSO-*d*₆, δ) 163.7, 152.7, 147.1, 140.9, 137.7, 132.2, 129.3, 128.7, 128.3, 128.2, 127.6, 126.2, 125.3, 121.9, 119.7, 98.7, 37.7,

23.5; IR (ATR) 3196, 3186, 3095, 1676, 1580, 1569, 1514, 1487, 1401, 1328 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}^{81}\text{Br}^{35}\text{Cl}$: 529.8955. Found: 529.8951.



tert-Butyl 8-Bromo-5-((4-chloro-2-iodophenyl)amino)-1-oxo-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (177) To a suspension of aminoquinoline **176** (185 mg, 350 μmol) in 35 mL of THF at 0 $^\circ\text{C}$, were added a solution of Boc_2O (76.4 mg, 350 μmol) in 5 mL of THF and solid DMAP (47.0 mg, 385 μmol). After 5 hours, a saturated aqueous NH_4Cl

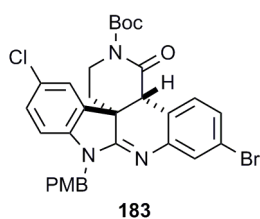
solution was added and the mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and the crude material was purified by silica gel column chromatography (CH_2Cl_2) to give the titled compound (191 mg, 87%) as a yellow solid; mp. 150 $^\circ\text{C}$ (decomp.); ^1H NMR (CDCl_3 , δ) 8.78-8.76 (m, 2H), 7.95 (d, 1H, $J = 1.9$ Hz), 7.77 (d, 1H, $J = 2.3$ Hz), 7.45 (dd, 1H, $J = 9.0, 1.9$ Hz), 7.37 (dd, 1H, $J = 8.9, 2.3$ Hz), 6.99 (s, 1H), 4.11 (t, 2H, $J = 5.9$ Hz), 2.97 (t, 2H, $J = 5.9$ Hz), 1.62 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 162.1, 151.9, 150.2, 147.4, 138.3, 137.7, 133.3, 129.6, 129.2, 128.5, 127.9, 127.7, 124.3, 123.7, 120.7, 120.0, 89.8, 84.0, 42.7, 28.1, 23.9; IR (ATR) 3403, 3386, 2979, 1759, 1713, 1693, 1584, 1517, 1402, 1145 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3^{81}\text{Br}^{35}\text{Cl}$: 629.9479. Found: 629.9476.



tert-Butyl 8-Bromo-5-((4-chloro-2-iodophenyl)(4-methoxybenzyl)amino)-1-oxo-3,4-dihydrobenzo[c][2,6]naphthyridine-2(1H)-carboxylate (182) To a solution of aminoquinoline **177** (4.65 g, 7.40 mmol) in 74 mL of THF at 0 $^\circ\text{C}$, were added *p*-methoxybenzyl iodide (2.39 g, 9.62 mmol)* and a suspension of NaH (60% wt, 326 mg, 8.14 mmol) in 37 mL of DMF. After 3

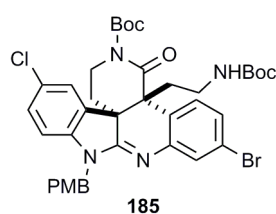
hours, a saturated aqueous NaHCO_3 solution was added to the reaction mixture. The aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ("hexane/AcOEt = 10/0 to 9/1) to give the titled compound (4.99 g, 90%) as an yellow amorphus; ^1H NMR (CDCl_3 , δ) 8.73 (d, 1H, $J = 9.2$ Hz), 8.07 (d, 1H, $J = 1.7$ Hz), 7.96 (d, 1H, $J = 2.0$ Hz), 7.51 (dd, 1H, $J = 9.2, 2.0$ Hz), 7.38 (d, 2H, $J = 8.6$ Hz), 7.11 (dd, 1H, $J = 8.6, 2.3$ Hz), 6.74 (d, 2H, $J = 8.6$ Hz), 6.40 (dd, 1H, $J = 8.6, 1.7$ Hz), 5.11 (br s, 2H), 3.78-3.74 (m, 5H), 2.16 (br s, 2H), 1.56 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 162.6, 158.5, 155.7, 151.6, 147.4, 146.8, 140.2, 134.9, 132.4, 130.8, 130.0, 129.9, 129.6, 129.4, 128.9, 127.8, 127.3, 123.5, 120.8, 113.3, 99.1, 83.8, 55.1, 54.2, 43.5, 28.0, 26.1; IR (ATR) 2979, 2934, 1766, 1715, 1483, 1510, 1464, 1300, 1145 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{29}\text{N}_3\text{O}_4^{81}\text{Br}^{35}\text{Cl}$: 750.0054. Found: 750.0054.

* *p*-Methoxybenzyl iodide was prepared by the reported procedure (Bilodeau, F.; Dubé, L.; Deslongchamps, P. *Tetrahedron* **2003** 59, 2781.).



tert-Butyl (4aRS,14bRS)-12-Bromo-6-chloro-9-(4-methoxybenzyl)-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (183) To a solution of aminoquinoline **182** (3.70 g, 4.94 mmol) in 50 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added $^n\text{BuLi}$ (1.60 M in $^n\text{hexane}$, 3.40 mL, 5.43 mmol) in a dropwise manner over 10 minutes. After an hour, a saturated aqueous NH_4Cl

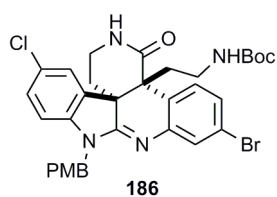
solution was added to the reaction mixture and the aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography ($^n\text{hexane}/\text{AcOEt} = 100/$ to $85/15$) to give the titled compound (2.30 g, 75%) as a yellow amorphous; ^1H NMR (CDCl_3 , δ) 7.44 (d, 1H, $J = 2.0$ Hz), 7.26-7.23 (m, 2H), 7.21-7.19 (m, 3H), 7.15 (d, 1H, $J = 1.7$ Hz), 6.85 (d, 2H, $J = 8.6$ Hz), 6.70 (d, 1H, $J = 8.6$ Hz), 5.18 (d, 1H, $J = 15.5$ Hz), 4.85 (d, 1H, $J = 15.5$ Hz), 3.90 (s, 1H), 3.78 (s, 3H), 3.69-3.68 (m, 2H), 2.39-2.36 (m, 1H), 1.60 (s, 9H), 1.46 (dd, 1H, $J = 9.9, 7.6$ Hz); ^{13}C NMR (CDCl_3 , δ) 169.1, 166.9, 159.1, 152.9, 145.5, 143.2, 132.1, 129.2, 128.6, 128.4, 127.8, 127.5, 127.4, 127.0, 123.9, 122.6, 118.5, 114.3, 110.2, 84.0, 55.2, 48.5, 44.3, 43.7, 42.3, 28.0, 25.6; IR (ATR) 2981, 1768, 1719, 1645, 1607, 1577, 1472, 1433, 1370, 1294, 1248 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_3\text{O}_4^{81}\text{Br}^{35}\text{Cl}$: 624.1088. Found: 624.1080.



tert-Butyl (4aSR,14bRS)-12-Bromo-14b-(2-((tert-butoxycarbonyl)amino)ethyl)-6-chloro-9-(4-methoxybenzyl)-1-oxo-1,3,4,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridine-2(9H)-carboxylate (185) To a solution of lactam **183** (44.8 mg, 71.9 μmol) in 1.4 mL of THF and 150 μL of DMPU at $-78\text{ }^{\circ}\text{C}$, was added KHMDS (1.0 M in THF, 86.3 μL , 86.3 μmol). After a minute, *N*-Boc

1,2,3-oxathiazolidine 2,2-dioxide (22.5 mg, 101 μmol)* was added and the reaction mixture was stirred for 3 minutes at the same temperature. Then the mixture was immediately warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 20 minutes. A saturated aqueous NH_4Cl solution was added and the resultant mixture was extracted with AcOEt twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel preparative thin-layer chromatography ($^n\text{hexane}/\text{AcOEt} = 7/3$) to give the titled compound (40.7 mg, 74%) as a colorless amorphous; ^1H NMR (CDCl_3 , δ) 7.41 (d, 1H, $J = 2.0$ Hz), 7.28 (d, 2H, $J = 8.9$ Hz), 7.19-7.18 (m, 2H), 7.05 (br s, 1H), 7.02 (d, 1H, $J = 8.3$ Hz), 6.87 (d, 2H, $J = 8.9$ Hz), 6.69 (br d, 1H, $J = 8.6$ Hz), 5.09 (d, 1H, $J = 15.8$ Hz), 4.93 (d, 1H, $J = 15.8$ Hz), 4.37-4.35 (m, 1H), 3.77 (s, 3H), 3.70-3.68 (m, 2H), 3.07-3.05 (m, 1H), 2.78-2.75 (m, 1H), 2.57-2.51 (m, 1H), 1.83-1.81 (m, 1H), 1.59 (s, 9H), 1.50-1.47 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (CDCl_3 , δ) 167.4, 159.2, 155.4, 153.3, 145.2, 143.3, 130.2, 129.2, 128.7, 128.53, 128.48, 128.1, 127.4, 127.2, 124.1, 122.9, 122.3, 114.3, 114.2, 110.4, 83.8, 78.7, 55.2, 51.9, 50.0, 44.3, 42.4, 37.7, 31.7, 28.3, 28.0, 27.4; IR (ATR) 3449, 2979, 1766, 1707, 1645, 1606, 1576, 1513, 1368, 1149 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{38}\text{H}_{43}\text{N}_4\text{O}_6^{81}\text{Br}^{35}\text{Cl}$: 767.2034. Found: 767.2032.

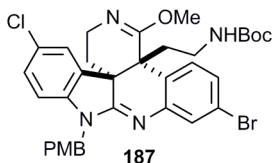
* *N*-Boc 1,2,3-oxathiazolidine 2,2-dioxide was prepared by the reported procedure (Moss, T. A.; Alonso, B.; Fenwick D. R.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 568.).



186

tert-Butyl (2-((4aSR,14bRS)-12-Bromo-6-chloro-9-(4-methoxybenzyl)-1-oxo-1,2,3,4,9,14b-hexahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-14b-yl)ethyl)carbamate (186) To a solution of pentacycle **185** (716 mg, 935 μmol) in 9 mL of CH_2Cl_2 at 0 $^\circ\text{C}$, was added 1 mL of TFA. The reaction mixture was stirred at the same temperature for 30 minutes. A saturated aqueous NaHCO_3 solution

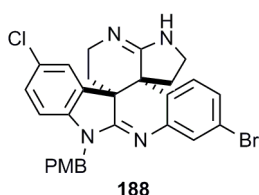
was added and the resultant mixture was extracted with CHCl_3 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (n hexane/ AcOEt = 8/2 to 6/4) to give the titled compound (499 mg, 80%) as a colorless amorphous; ^1H NMR (CDCl_3 , δ) 7.39 (d, 1H, J = 1.7 Hz), 7.29-7.28 (m, 3H), 7.19-7.18 (m, 2H), 6.86 (d, 2H, J = 8.9 Hz), 6.71 (d, 1H, J = 8.9 Hz), 6.38 (br s, 1H), 5.11 (d, 1H, J = 15.5 Hz), 5.01 (s, 1H), 4.92 (d, 1H, J = 15.5 Hz), 3.77 (s, 3H), 3.51 (ddd, 1H, J = 12.4, 12.4, 5.3 Hz), 3.36-3.35 (m, 1H), 2.91-2.85 (m, 1H), 2.55-2.52 (m, 1H), 1.84-1.82 (m, 1H), 1.56-1.50 (m, 1H), 1.44-1.35 (m, 10H); ^{13}C NMR (CDCl_3 , δ) 172.5, 167.3, 159.2, 155.5, 145.2, 143.5, 129.8, 129.2, 128.8, 128.4, 128.3, 127.6, 127.3, 127.1, 124.4, 123.0, 122.6, 114.3, 110.3, 78.6, 55.2, 48.89, 48.86, 38.2, 37.6, 32.2, 28.4, 25.5; IR (ATR) 3310, 2977, 1699, 1646, 1576, 1513, 1457, 1366, 1249, 1174 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{32}\text{H}_{35}\text{N}_4\text{O}_4^{79}\text{Br}^{35}\text{Cl}$: 665.1531. Found: 665.1533.



187

tert-Butyl (2-((4aSR,14bRS)-12-Bromo-6-chloro-1-methoxy-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[c]indolo[3,2-j][2,6]naphthyridin-14b-yl)ethyl)carbamate (187) To a suspension of lactam **186** (32.9 mg, 49.4 μmol) and NaHCO_3 (20.8 mg, 247 μmol) in 0.5 mL of CH_2Cl_2 at ambient temperature, was

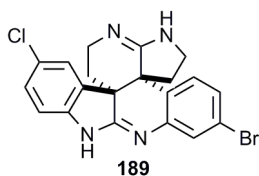
added $\text{Me}_3\text{O}\cdot\text{BF}_4$ (7.7 mg, 52.1 μmol) in two portions over an hour. After an additional hour, a saturated aqueous NaHCO_3 solution was added and the resultant mixture was extracted with CHCl_3 twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel preparative thin-layer chromatography (n hexane/ AcOEt = 5/5) to give the titled compound (9.8 mg, 29%) as a colorless oil; ^1H NMR (CDCl_3 , δ) 7.35 (br s, 1H), 7.28 (d, 2H, J = 8.6 Hz), 7.15-7.13 (m, 3H), 6.97 (br s, 1H), 6.86 (d, 2H, J = 8.6 Hz), 6.67 (d, 1H, J = 8.0 Hz), 5.15 (d, 1H, J = 15.5 Hz), 4.86 (d, 1H, J = 15.5 Hz), 3.96 (br s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.68-3.55 (m, 2H), 3.16-3.14 (br m, 1H), 2.68-2.66 (br m, 1H), 2.33-2.29 (m, 1H), 1.85-1.80 (m, 1H), 1.52-1.51 (br m, 1H), 1.33-1.20 (m, 10H); ^{13}C NMR (CDCl_3 , δ) 168.2, 159.2, 145.3, 143.3, 130.6, 128.7, 128.3, 128.2, 127.7, 127.1, 127.0, 125.8, 124.7, 122.2, 114.3, 110.0, 78.8, 55.2, 53.1, 48.7, 45.0, 44.2, 41.9, 38.3, 32.6, 28.3, 26.4; IR (ATR) 3451, 2977, 2943, 1705, 1671, 1644, 1605, 1575, 1512, 1433, 1366, 1247, 1169 cm^{-1} ; HRMS (MH^+) calcd for $\text{C}_{34}\text{H}_{37}\text{N}_4\text{O}_4^{81}\text{Br}^{35}\text{Cl}$: 681.1666. Found: 681.1659.



188

(3aRS,13bSR)-6-Bromo-12-chloro-9-(4-methoxybenzyl)-1,2,3,9,14,15-hexahydrobenzo[c]indolo[3,2-j]pyrrolo[3,2-e][2,6]naphthyridine (188) To a solution of methyl imidate **187** (55.3 mg, 81.3 μmol) in 4.5 mL of CH_2Cl_2 at ambient temperature, was added 0.5 mL of TFA. After 4 hours, a saturated aqueous

NaHCO₃ solution was added and the resultant mixture was extracted with CHCl₃ twice. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. A solution of the crude material in 5 mL of toluene was heated to 100 °C for 21 hours. After cooled to ambient temperature, the reaction mixture was evaporated and direct NH silica gel column chromatography (CHCl₃/MeOH = 99/1) gave the titled compound (34.3 mg, 2 steps, 77%) as a colorless amorphus; ¹H NMR (CDCl₃, δ) 7.41 (d, 1H, *J* = 2.0 Hz), 7.24 (d, 2H, *J* = 8.6 Hz), 7.16-7.15 (m, 2H), 7.12 (d, 1H, *J* = 2.0 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 6.84 (d, 2H, *J* = 8.6 Hz), 6.64 (d, 1H, *J* = 8.3 Hz), 5.06 (d, 1H, *J* = 15.8 Hz), 5.00 (d, 1H, *J* = 15.8 Hz), 4.66 (br s, 1H), 3.77 (s, 3H), 3.51 (dd, 1H, *J* = 12.6, 8.3 Hz), 3.44 (ddd, 1H, *J* = 12.6, 12.6, 5.0 Hz), 3.36-3.32 (m, 2H), 2.39 (ddd, 1H, *J* = 12.6, 12.6, 6.3 Hz), 1.90-1.88 (m, 1H), 1.66 (dd, 1H, *J* = 12.0, 5.7 Hz), 1.39 (dd, 1H, *J* = 13.5, 4.0 Hz); ¹³C NMR (CDCl₃, δ) 167.8, 165.3, 159.0, 144.6, 130.5, 128.7, 128.4, 128.2, 127.6, 127.1, 126.91, 126.89, 125.1, 124.8, 121.8, 114.2, 110.0, 55.2, 50.8, 48.5, 47.2, 44.1, 39.0, 32.6, 26.1; IR (ATR) 3189, 2932, 2859, 1640, 1604, 1574, 1512, 1432, 1369, 1247, 1173 cm⁻¹; HRMS (MH⁺) calcd for C₂₈H₂₅N₄O⁸¹Br³⁵Cl: 549.0880. Found: 549.0880.



(3aRS,13bSR)-6-Bromo-12-chloro-1,2,3,9,14,15-hexahydrobenzo[c]indolo[3,2-e]pyrrolo[3,2-e][2,6]naphthyridine (189) To a solution of haxacycle **188** (29.5 mg, 53.8 μmol) in 1.8 mL of anisole, was added 0.2 mL of H₃PO₄. The reaction mixture was heated to 120 °C for 48 hours. After cooled to ambient temperature,

0.8 mL of H₂O was added. Hexane was added to the mixture and after vigorous stirring the organic layer was removed. This washing was repeated additionally three times. To the mixture was added 3 mL of THF and the resultant solution was basified with a 2.0 M aqueous NaOH solution. The separated aqueous layer was extracted with mixture of THF and AcOEt (1:1) and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by NH silica gel preparative thin-layer chromatography (AcOEt/MeOH = 95/5) to give the titled compound (13.8 mg, 60%) as a colorless solid; mp. 320 °C (decomp.); ¹H NMR (CF₃CO₂D, δ) 7.59-7.52 (m, 3H), 7.39 (d, 1H, *J* = 8.4 Hz), 7.29 (d, 1H, *J* = 1.4 Hz), 7.05 (d, 1H, *J* = 8.3 Hz), 3.81-3.79 (m, 3H), 3.70-3.68 (m, 1H), 2.71-2.69 (m, 1H), 2.22-2.19 (m, 2H), 1.96-1.94 (m, 1H); ¹³C NMR (CF₃CO₂D, δ) 169.5, 168.2, 140.7, 136.1, 134.6, 133.1, 129.3, 128.4, 127.8, 126.4, 126.3, 122.4, 118.2, 53.1, 52.2, 45.9, 40.5, 32.8, 26.3; IR (ATR) 3193, 2931, 1734, 1652, 1447, 1236, 1213 cm⁻¹; HRMS (MH⁺) calcd for C₂₀H₁₇N₄⁷⁹Br³⁵Cl: 427.0325. Found: 427.0330.

発表論文目録

第二章 ヨウ化サマリウム(II)による還元的環化反応を鍵反応とする骨格構築

1. “Synthesis of 2-iminoindolines via samarium diiodide mediated reductive cyclization of carbodiimides”

Takayuki Ishida, Chihiro Tsukano, Yoshiji Takemoto*, *Chem. Lett.* **2012**, 41(1), 44-46

2. “Synthetic study of perophoramidine: construction of pentacyclic core structure via SmI₂-mediated reductive cyclization”

Takayuki Ishida, Yoshiji Takemoto*, *Tetrahedron* **2013**, 69(23), 4517-4523

第三章 脱芳香族共役付加反応を鍵反応とする骨格構築

3. “Dearomatizing conjugate addition to quinolinyl amidines for the synthesis of dehaloperophoramidine through tandem arylation and allylation”

Takayuki Ishida, Hideo Ikota, Kei Kurahashi, Chihiro Tsukano, Yoshiji Takemoto*
Angew. Chem. Int. Ed. **2013**, 52(39), 10204-10207

その他関連研究における発表論文

4. “Synthesis of indolo[2,3-b]quinolines by palladium-catalyzed annulation of unsaturated isothioureas”

Hiroshi Takeda, Takayuki Ishida, Yoshiji Takemoto*, *Chem. Lett.* **2009**, 38(8), 772-773

5. “Synthesis of 3,3-disubstituted oxindoles through Pd-catalyzed intramolecular cyanoamidation”

Yoshizumi Yasui, Haruhi Kamisaki, Takayuki Ishida, Yoshiji Takemoto*
Tetrahedron **2010**, 66(11), 1980-1989

謝辞

本研究にあたり終始御懇篤なる御指導御鞭撻を賜り、また主査として本論文の査読を担当して頂いた京都大学大学院薬学研究科 竹本佳司教授に衷心より感謝の誠を捧げ御礼申し上げます。

また、本研究を行うにあたり多大なる御助言御協力を頂きました京都大学大学院薬学研究科 塚野千尋助教に心より感謝申し上げます。加えて、有益な御助言御協力を頂きました京都大学大学院薬学研究科 高須清誠教授、小林祐輔特定助教、猪熊翼特定助教（現 徳島大学大学院ヘルスバイオサイエンス研究部特任助教）に深く感謝申し上げます。

共に研究に従事し、多くの御指導と御助言を頂いた安藤（旧姓上崎）春陽博士（現 武田薬品工業株式会社）並びに竹田寛修士（現 独立行政法人医薬品医療機器総合機構）、ならびに日夜討論を交わして共に研究に取り組んだ倉橋慧修士（現 第一三共株式会社）、伊古田秀夫学士に心より感謝の意を捧げます。また、同級生として切磋琢磨した東巧博士をはじめとして、京都大学大学院薬学研究科薬品分子化学分野の諸氏に心より感謝いたします。

副査として本論文の査読を担当して頂き、多大なる御教示を賜りました京都大学大学院薬学研究科 川端猛夫教授、ならびに高須清誠教授に心より御礼申し上げます。

また、本研究の遂行に際して、元素分析の実施に御協力頂いた京都大学有機微量元素分析総合施設の諸氏に心より感謝申し上げます。

最後に、長きに亘る学生生活を物心両面で支えて頂いた家族をはじめとして、親族ならびに友人の方々に深く感謝致します。

2014年3月

石田 貴之