

立体網羅的誘導体供給を志向した  
1,4a-di-*epi-ent*-pancratistatin の全合成

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## 略号表

aq	aqueous
Ac	acetyl
Bn	benzyl
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
DMAP	<i>N,N</i> -dimethyl-4-aminopyridine
DMF	<i>N,N</i> -dimethylformamide
equiv.	equivalent
Et	ethyl
ee	enantiomeric excess
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
Me	methyl
mp	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
ppm	parts per million
rt	room temperature
sat	saturated
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl

THF tetrahydrofuran  
TMS trimethylsilyl  
Tf trifluoromethanesulfonyl  
Tr triphenylmethyl  
TFA trifluoroacetic acid

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## 序論

Pancreatistatin は特徴的な構造（6連続不斉中心を持つシクロヘキサン環を含む縮環構造）と魅力的な生物活性（アポトーシス誘導を介する強力な抗腫瘍活性）を持つことから、単離以来約40年間注目されてきた。実際、4例のラセミ体合成と13例の光学活性体合成および多数の誘導体合成が国内外から報告されている。このことは、本研究の重要性と国際的な注目度を端的に示している。しかしながら、合成された誘導体は限られており、その構造活性相関の情報は不十分である。また、Fas受容体を介するカスパーゼ-3活性化の関与を示唆する報告はあるものの、生物活性の詳細な発現機構は不明である。更なる解明のために様々な誘導体を用いて活性を評価することが必要である。これまでに報告された合成法はターゲットの立体配置に特化した合成法で、立体異性体の合成には利用できないという問題点がある。したがって、徹底的な構造活性相関研究や生物活性発現機構の解明などを達成するためには短工程かつフレキシブルな立体網羅的合成法の開発が必要である。

本研究では市販の糖類から **pancratistatin** の様々な立体異性体・誘導体を網羅的かつ効率的に合成することを計画した。**Pancratistatin** 誘導体のアポトーシス誘導について網羅的構造活性相関が可能となり詳細な情報が得られれば、より強力な抗腫瘍活性を持つ誘導体が発見され、新たな抗がん剤のシードとなると期待した。また、活性発現に関与しない官能基を特定できれば、その位置に光応答官能基などを導入してアポトーシス誘導機構を解明するために使用する分子プローブを開発できる。さらには、これまでに合成されたことのない新たな誘導体の中からは、新たな生物活性を持つものが発見され得るだろう。**phenanthridinone** 骨格は多くのアルカロイドに含まれる基本骨格なので、開発した **phenanthridinone** 骨格の新規構築法は様々なアルカロイド合成へ応用できると期待できる。

本論文は3つの章から構成される。

第1章は、本研究の研究背景である。これまでの **pancratistatin** に関する研究と本研究での先行研究を紹介した上で、本研究の合成戦略を述べる。

第2章は、**pancratistatin** 立体異性体の網羅的合成研究である。まず、モデル研究でラジカ

ル環化反応、ニッケル触媒を用いたカップリング反応および有機銅試薬による共役付加反応をそれぞれ検討した。有機銅試薬による共役付加反応の検討で最も良い結果が得られたので、実際に **pancratistatin** 立体異性体の合成に応用した。また、合成した **pancratistatin** 立体異性体及び合成中間体の生物活性を評価した。

第 3 章では、**phenanthridinone** 三環性骨格合成法の一般化に関する検討について述べる。第 2 章で述べた **pancratistatin** 立体異性体合成で新たに開発した骨格合成反応をさらに最適化した上、適用範囲を調べた。本合成法は **pancratistatin** 以外の天然物や誘導体合成に合成できると期待した。

## 第 1 章 研究背景

## 第1節. Pancratistatin 及びその類縁体

Pancratistatin (**1-1**) は1984年に Pettit らにより *Pancreaticum littoral* の球根から単離・構造決定された amaryllidaceae アルカロイドであり<sup>1)</sup>、電子豊富な芳香環 (A 環)、多くの sp<sup>2</sup> 原子の存在によりゆがんだ6員環ラクタム (B 環) 及び、高度に水酸化された6連続不斉中心からなる6員環 (C 環) という興味深い構造的特徴を持った天然物である (Figure 1)。類似の構造を持つ 7-deoxypancratistatin (**1-2**)<sup>1)</sup> や narciclasine (**1-3**)<sup>2)</sup>、lycoricidine (**1-4**)<sup>3)</sup> も含め、300 を超える数の化合物が単離されている。Amaryllidaceae アルカロイドは有機合成化学者の興味を大きく引き付けており、その中でも pancratistatin (**1-1**) は強力な抗腫瘍活性<sup>5)</sup> や抗ウイルス活性を有する<sup>4), 5)</sup> ことから創薬シーズとして期待されている。**1-1** の抗腫瘍活性は腫瘍細胞に対するアポトーシス誘導に起因するものと考えられているがその詳細なメカニズムは明らかになっていない。種々の構造活性相関研究<sup>6)</sup> により、B 環と C 環のトランス縮環構造、及び 2,3,7 位の水酸基の存在が活性発現に重要であることが示唆されているが、C 環の各炭素の絶対立体配置がどのように生物活性に寄与しているかは不明であり、メカニズムの更なる解明のために多くの合成研究がなされている。

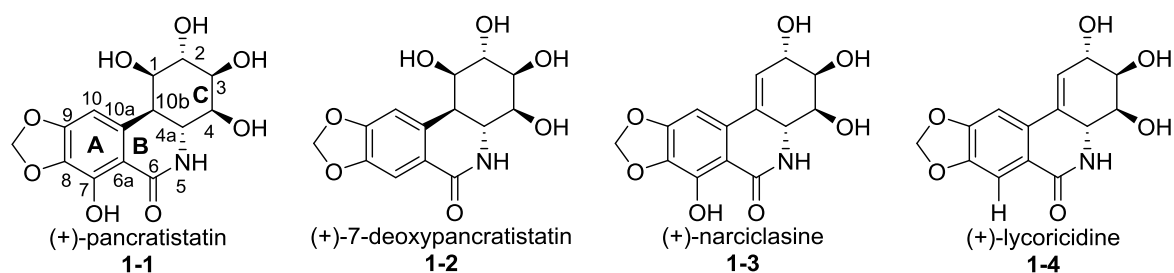
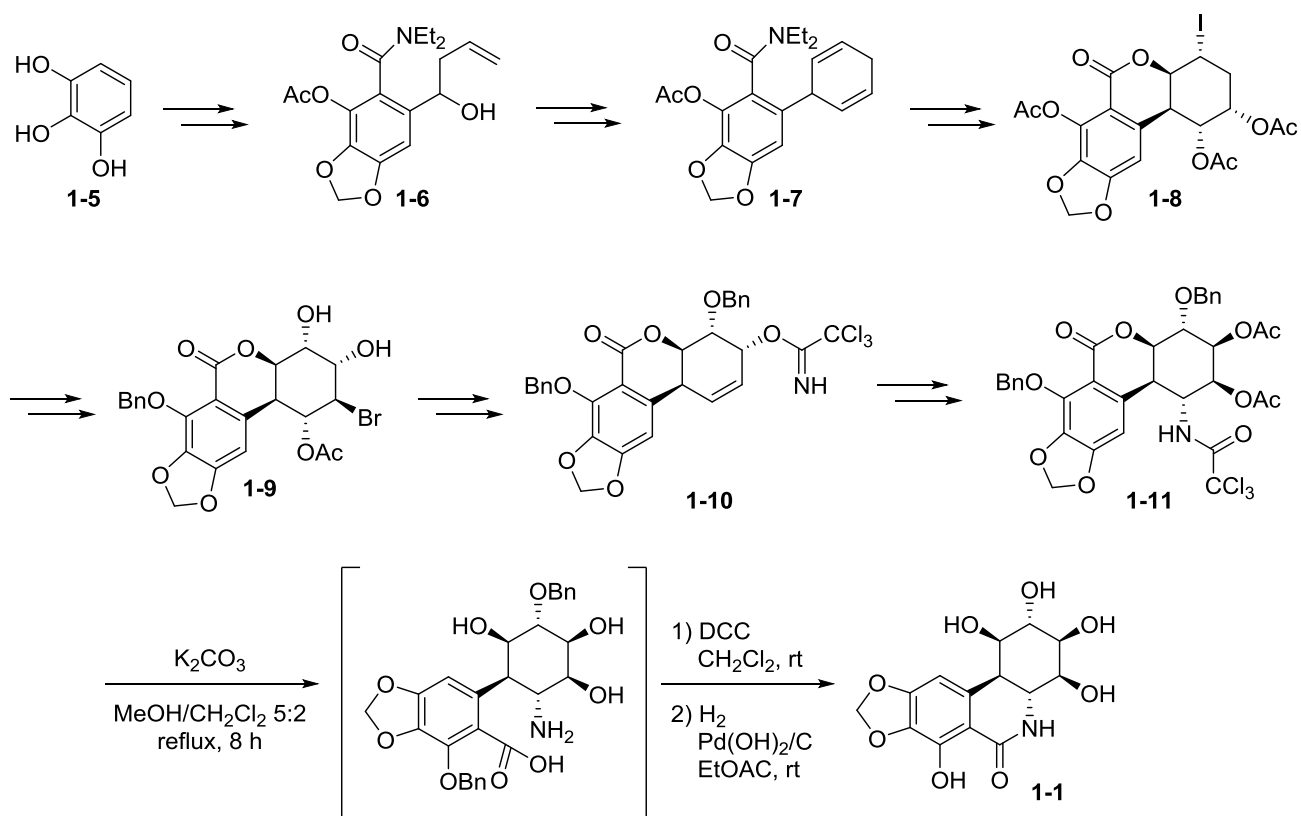


Figure 1.1 The chemical structures of major amaryllidaceae alkaloids.

## 第2節. Pancratistatin の合成例

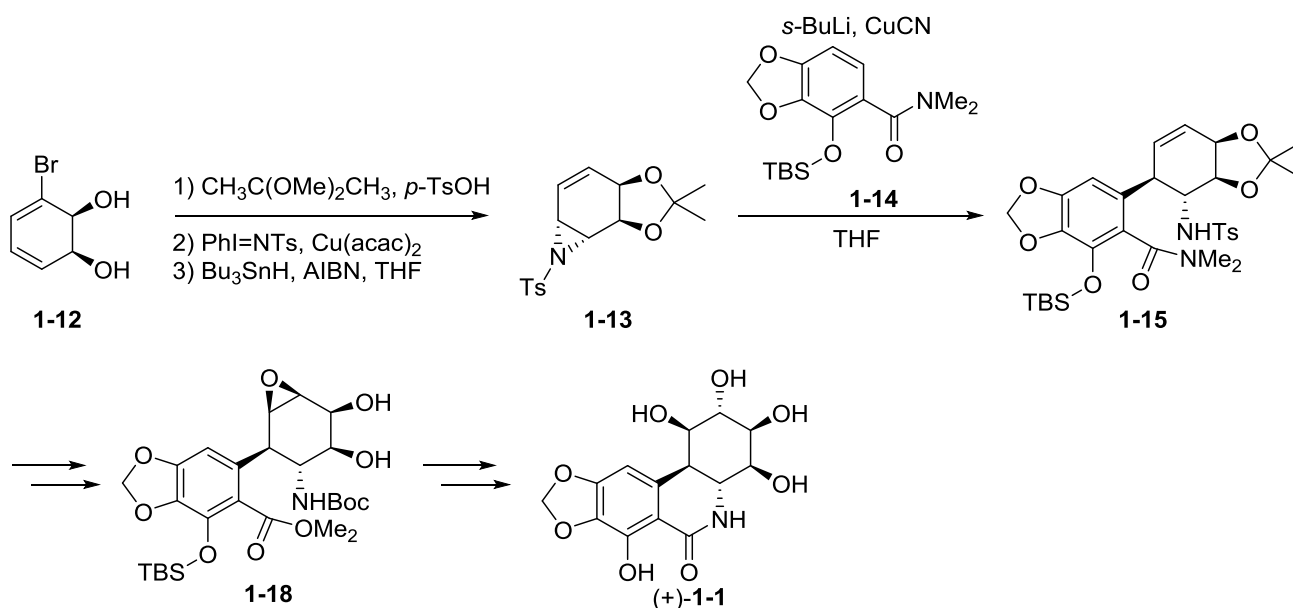
1989年に Danishefsky らによって、Scheme 1.2 に示した合成ルートで初のラセミ体 pancratistatin (**1-1**) の全合成が達成された<sup>7a)</sup>。Pyrogallol (**1-5**) を出発原料として、芳香環上にカルボン酸アミド及び6員環前駆体となるアリルアルコール構造を導入した**1-6**へと誘導し、シクロヘキサジエン部位を導入した。得られた**1-7**のヨードラクトン化とジヒドロキシル化によって**1-8**を合成し、種々官能基化を経て6置換化合物**1-9**を得た。その後、水酸基をトリクロロイミドイル基で保護した後に還元的に二重結合を導入し**1-10**を合成した。最後に各種保護基の除去とラクトン部位のラクタムへの巻き直しを行い、**1-1**の初の全合成を達成した。





**Scheme 1.2** Total synthesis of (±)-pancratistatin (**1-1**) reported by Danshefsky.

その後、光学活性体を容易に入手可能な **1-12** をキラルプールとして利用した **1-1** の光学活性体の全合成が Hudlicky らにより報告された (**Scheme 1.3**)<sup>7b)</sup>。まず **1-12** の 1,2-ジオール部位をアセタール保護し、2 置換オレフィン部位に立体特異的にアジリジン環を導入した後ラジカル還元条件で脱ブロモ化することで **1-13** を合成した。別途合成した芳香環ユニット **1-14** から調製される有機銅試薬と **1-13** を反応させることで両ユニットが連結され窒素官能基も導入された **1-15** を得た。さらに残ったオレフィン部位をエポキシ化し、これを足掛かりとすることで *trans*-1,2-ジオール構造へと誘導し、(+)-**1-1** の全合成を達成した。



**Scheme 1.3** Total synthesis of (+)-pancratistatin **1-1** reported by Hudlicky.

それ以降、現在までに多くの合成化学者によって本化合物の合成が多数報告されている (Table 1.1)<sup>7)</sup>。しかし、これらの合成戦略はそのほとんどが三環性骨格を構築した後、合成終盤に C 環の不斉点を順次導入するものであった。複雑な構造が構築された後に不斉点を導入するこれらの戦略では、立体選択性の発現に基質の立体構造による影響を大きく受けるため、多様な立体構造の異性体を網羅的に構築することは困難であると予想される。このことから現在までに確立した合成法によって水酸基の立体配置が異なる種々の pancratistatin 誘導体を網羅的に合成することは困難であり、当該骨格の新規な合成戦略の開拓が求められている。そこで本研究で著者は本骨格を持つ種々ジアステレオマーの網羅的合成を可能とする新しい合成手法の開発に取り組むこととした。具体的な合成戦略を次項に示す。

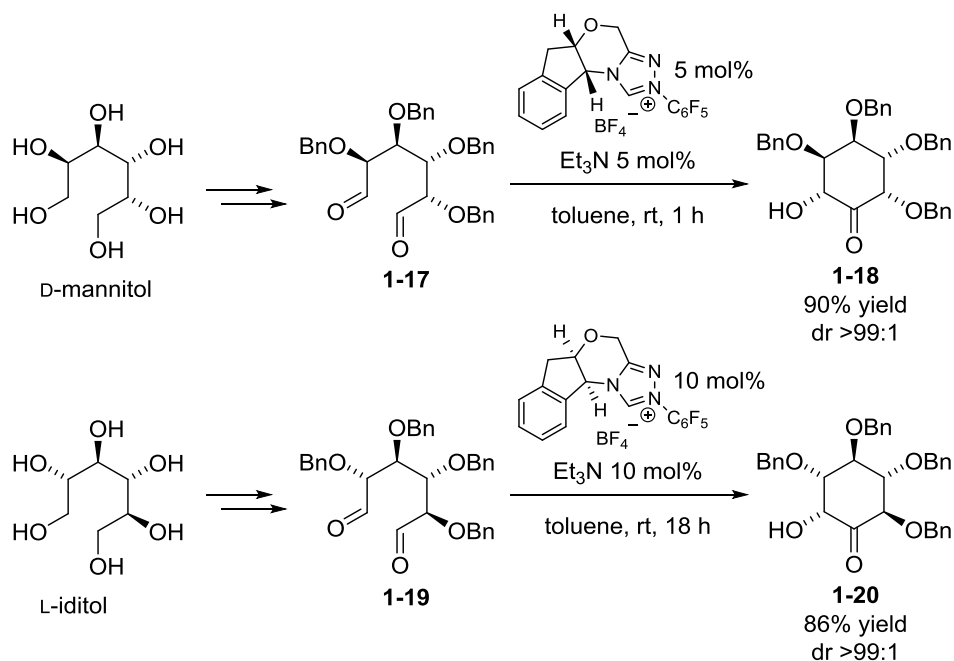
**Table 1.1** Summary of total and formal syntheses of pancratistatin.

Author	Year	Number of steps	Racemate or (+)	Ref
Danishefsky	1989	27	(±)	ref. 2a
Hudlicky	1995	14	(+)	ref. 2b
Trost	1995	20	(+)	ref. 2c
Haseltine	1997	24	(+)	ref. 2d
Magnus	1998	22	(+)	ref. 2e
Rigby	2000	23	(+)	ref. 2f
Pettit	2001	10	(+)	ref. 2g
Kim	2002	21	(±)	ref. 2h
Li	2006	13	(+)	ref. 2i
Madsen	2009	18	(+)	ref. 2j
Cho	2011	16	(±)	ref. 2k
Alonso	2012	14	(+)	ref. 2l
Sato	2013	18	(+)	ref. 2m
Ellman	2017	10	(+)	ref. 2n
Hudlicky	2017	14	(+)	ref. 2o
Sarlah	2017	9	(+)	ref. 2p
Liu	2022	10	(+)	Ref. 2q

### 第3節. NHC 触媒による不斉ベンゾイン反応

近年、含窒素複素環カルベン、いわゆる NHC を用いる新しい変換反応が盛んに研究されている。NHC を有機触媒として用いる反応には、極性転換を伴うものや、アシルアゾリウムを経由するものなどがある。所属研究室では、NHC 触媒による分子内ベンゾイン反応によって様々なイノソース立体異性体を合成する手法の開発に成功した (**Scheme 1.4**)<sup>8)</sup>。例

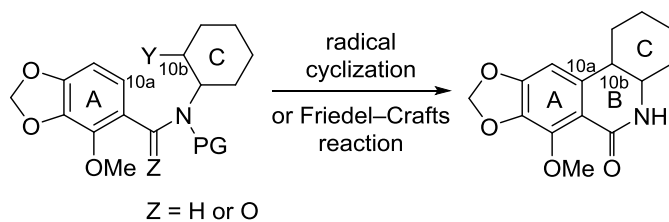
例えば、市販の D-mannitol から容易に調製可能なジアルデヒド **1-17** に対して NHC 触媒を用いるベンゾイン反応を行うと、キラルイノソース **1-18** が高収率かつ高立体選択的に得られる。D-mannitol の代わりに L-iditol を用いると、イノソース **1-20** が高収率かつ高立体選択的に合成できる。このように、原料に用いるアルジトールを変更するだけで様々な立体配置を持つイノソースが得られる。そこで、得られたイノソースを用いて **pancratistatin (1-1)** の C 環ユニット誘導体を合成すれば様々な **pancratistatin** 立体異性体が合成可能と考えた。



**Scheme 1.4** Chiral Inosose syntheses catalyzed by NHC-catalyst.

#### 第 4 節. 所属研究室における先行研究

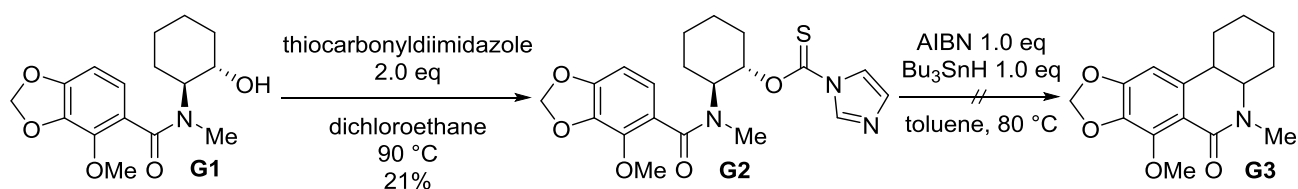
所属研究室では多数の立体中心を含む C 環部分はすでに開発した NHC 触媒による分子内ベンゾイン反応<sup>8)</sup>で得られる様々な立体を持つイノソースから **pancratistatin** 立体異性体を合成することとした。適切なカップリング反応で A 環と C 環を連結して B 環を構築することを計画した (**Scheme 1.5**)。本研究の開始当初、A 環と C 環を連結する C10a–C10b カップリング反応として以下の分子内ラジカル環化反応及び Friedel–Crafts 反応がすでに検討されていた。



**Scheme 1.5** Synthesis strategy of previous study.

#### 4.1 後藤による先行研究

後藤は基質 **G1** の水酸基にチオカルボニル基を導入しモデル基質 **G2** を合成した。Azobisisobutyronitrile (AIBN) 存在下トリブチルスズヒドريد ( $\text{Bu}_3\text{SnH}$ ) を用いて分子内ラジカルカップリングを試みたものの環化体は得られなかった (**Scheme 1.6**)。

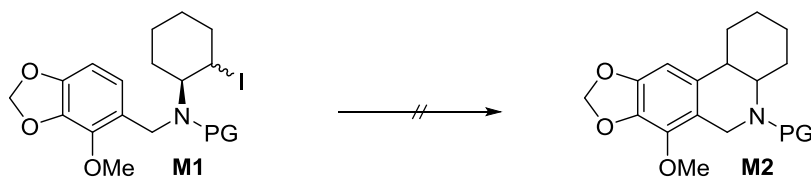


**Scheme 1.6** Goto's previous study

#### 4.2 益田による先行研究

益田は **M1a**、**M1b** を合成してラジカル環化反応による閉環を検討した (**Table 1.2**)。 **M1a** に対してラジカル反応開始剤として AIBN を用いて 100 °C で反応を行ったものの反応は進行しなかった (entry 1)。高温で反応を行うために V-40 を用いて 120 °C で反応させたが反応は進行しなかった (entry 2)。窒素上の保護基が異なる **M1b** を用いると目的の環化体とは異なる副生成物が生成した (entry 3)。

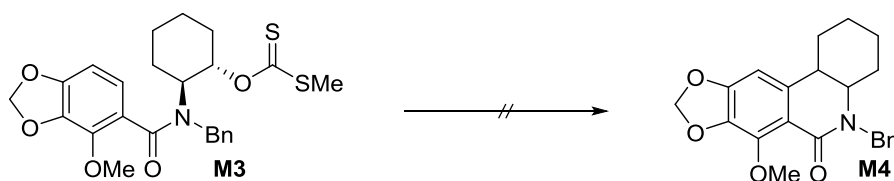
**Table 1.2** Radical reactions with **M1** by Masuda.



entry	<b>M1</b>	PG	condition	yield
1	<b>M1a</b>	<i>o</i> -Ns	AIBN (0.1 eq), Bu <sub>3</sub> SnH (5.0 eq), toluene, 100 °C, 15 h	0%
2	<b>M1a</b>	<i>o</i> -Ns	V-40 (0.1 eq), Bu <sub>3</sub> SnH (5.0 eq), PhCl, 120 °C, 10 h	0%
3	<b>M1b</b>	<i>p</i> -Ns	AIBN (0.5 eq), Bu <sub>3</sub> SnH (5.0 eq), toluene, 110 °C, 8 h	0%

益田は次に、ラジカル付加反応が進行しやすくするために A 環上の電子密度が **M1** より低下した **M3** を用いてラジカル閉環反応を検討した (**Table 1.3**)。反応開始剤として AIBN、還元剤として Bu<sub>3</sub>SnH を用いたところ、複雑な混合物が得られるのみで目的の環化体は観測されなかった (entry 1)。還元剤として tris(trimethylsilyl)silane (TTMSS) を用いたが、目的物は同様に得られなかった (entry 2)。次に、低温で利用できるトリエチルホウ素 (Et<sub>3</sub>B) をラジカル開始剤として用いて反応を行った。還元剤として Bu<sub>3</sub>SnH を用いたところ、TLC 上で何らかの反応の進行を確認できたが、目的の環化体は確認できなかった (entry 3)。還元剤を TTMSS に変更したが、やはり環化体は得られなかった (entry 4)。

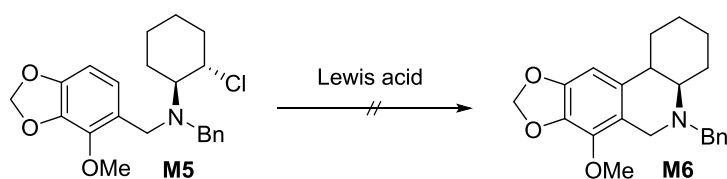
**Table 1.3** Radical reactions with **M3** by Masuda.



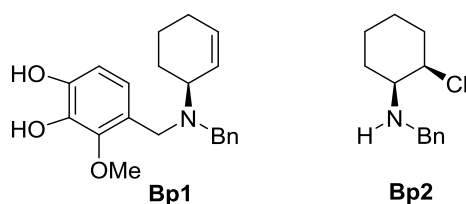
entry	condition	result
1	AIBN (0.1 eq), Bu <sub>3</sub> SnH (5.0 eq), toluene, 100 °C, 15 h	complex mixture
2	AIBN (0.5 eq), TTMSS (1.5 eq), toluene, 110 °C, 2 h	complex mixture
3	Et <sub>3</sub> B (2.0 eq), Bu <sub>3</sub> SnH (4.0 eq), CH <sub>2</sub> Cl <sub>2</sub> , rt, 4 h	complex mixture
4	Et <sub>3</sub> B (2.0 eq), TTMSS (3.0 eq), CH <sub>2</sub> Cl <sub>2</sub> , rt, 3 h	complex mixture

益田は Friedel–Crafts 型反応による環化の検討も行った (Table 1.4)。M5 に対してルイス酸として塩化アルミニウムを用いて反応を行ったところ二つの副生成物が得られた (entry 1)。副生成物の構造は  $^1\text{H}$  NMR と ESI–MS の結果から Bp1 と Bp2 と推定された。これらは反応中で生成した酸によるアセタール分解、及び電子豊富なベンジル位での開裂によって生成したものと考えられる。また、ルイス酸として酸化銀を用いて反応を行ったが目的物を得ることはできなかった (entries 2 and 3)。ルイス酸としてテトラフルオロホウ酸銀を用いて 75 °C で反応させた場合も目的物は得られなかった (entry 4)。

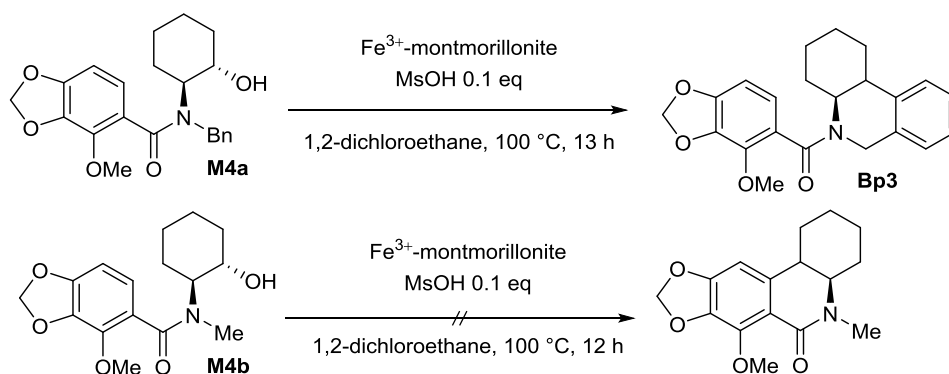
Table 1.4 Friedel–Crafts reactions with M5 by Masuda.



entry	condition	result
1	$\text{AlCl}_3$ (2.0 eq), toluene, 80 °C, 7 h	<b>Bp1, Bp2</b>
2	$\text{Ag}_2\text{O}$ (1.0 eq), MeCN, rt, 27 h	complex mixture
3	$\text{Ag}_2\text{O}$ (0.5 eq), MeCN, 80 °C, 27 h	complex mixture
4	$\text{AgBF}_4$ (1.0 eq), $\text{CF}_3\text{CH}_2\text{OH}$ , 75 °C, 5 h	complex mixture



また、益田は  $\text{Fe}^{3+}$ –montmorillonite と触媒量のメタンスルホン酸を用いる Friedel–Crafts 反応も検討した (Scheme 1.7)。アミドの Bn 保護体である M4a を反応条件に付したところ、目的の環化体を得ることはできず副生成物が生じた。副生成物の構造は  $^1\text{H}$  NMR と ESI–MS より、ベンジル基側の芳香環から閉環反応が進行した Bp3 と推定された。そこで閉環反応を起さないメチル基で保護した M4b を用いたが、反応は進行しなかった。

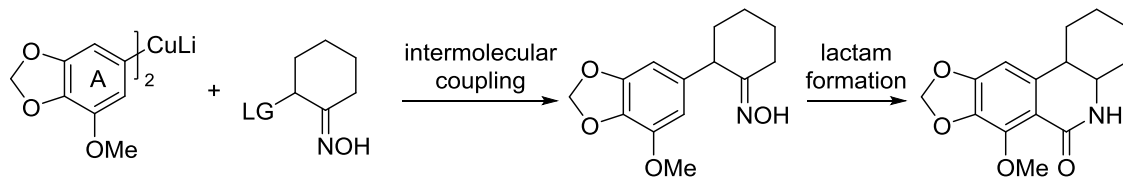
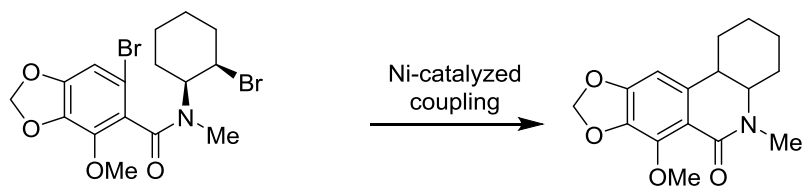
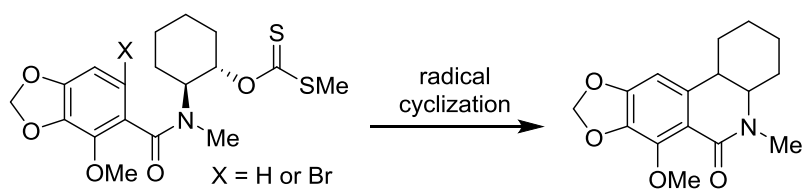
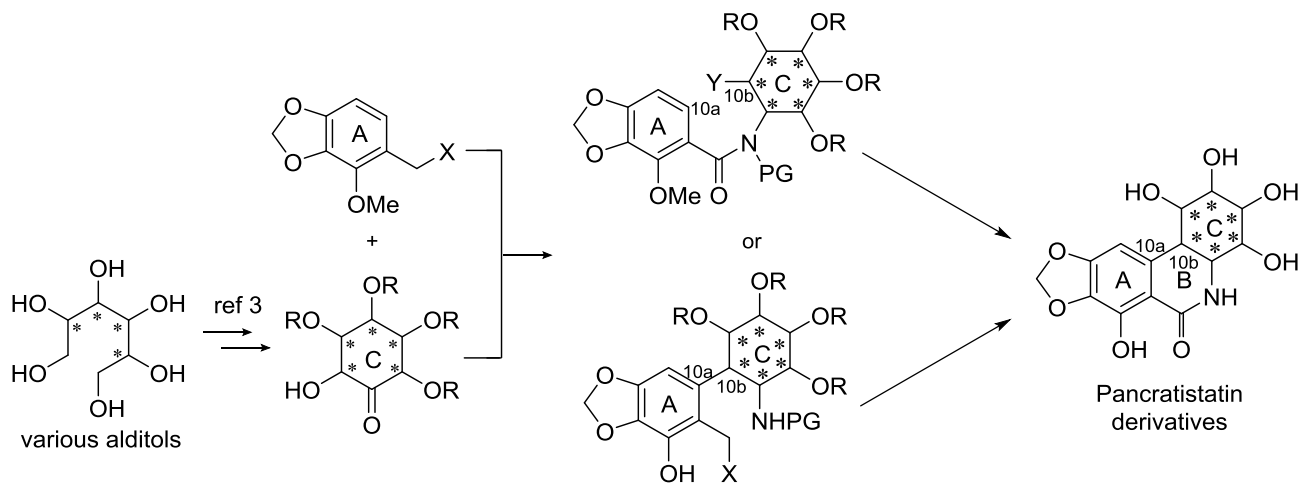


**Scheme 1.7** Friedel–Crafts reactions with **M4** by Masuda.

## 第5節 本研究の合成戦略

本研究では、A 環と C 環の炭素原子間の連結に分子内環化反応と分子間カップリング反応との二つのルートを試みた (**Scheme 1.8**)。分子内環化反応では、まず後藤と益田の先行研究の結果を踏まえた上でラジカル環化反応をさらに検討した。その後、近年に活発に研究されてきたニッケル触媒を用いる  $sp^2$  炭素- $sp^3$  炭素間のクロスカップリング反応を検討した。分子間カップリング反応は有機銅試薬による分子間共役付加反応を検討した。





**Scheme 1.8** Synthesis strategies of this study.

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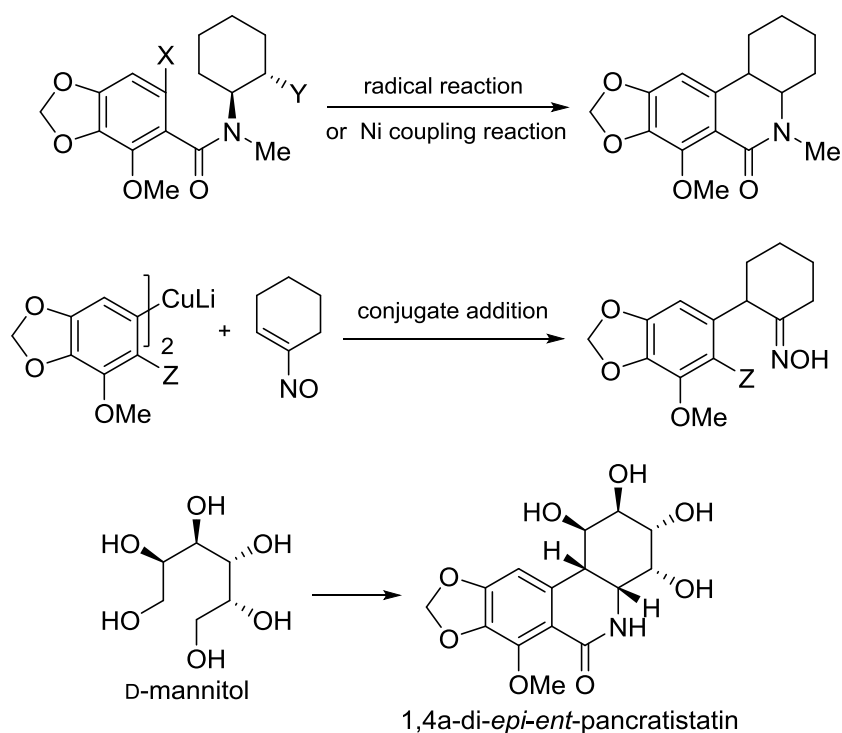
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## 第 2 章

### 立体網羅的誘導体供給を志向した **1,4a-di-*epi-ent*-pancratistatin** の全合成

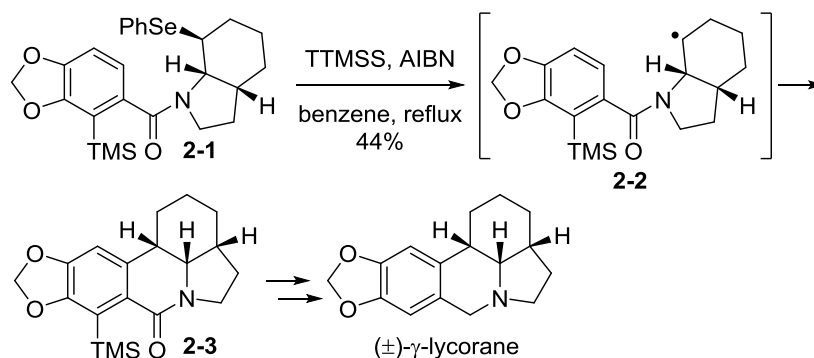
本章では、まず 1 章第 3 節の結果を踏まえたうえで行った分子内ラジカル閉環反応のさらなる検討と、ニッケル触媒を用いる分子内カップリング反応と分子間共役付加反応によるカップリング反応の検討についてまず述べる。残念ながら、これらの分子内環化反応は奏効しなかったため、分子間カップリングを検討した。その後、市販の安価な糖 D-mannitol から **pancratistatin** 立体異性体の合成を行った (**Figure 2.1**)。最後に、合成した **pancratistatin** 誘導体 1,4a-di-*epi-ent*-**pancratistatin** 及び合成中間体を用いて生物活性を評価した。



**Figure 2.1** Synthesis strategy.

## 第1節 ラジカル閉環反応の検討

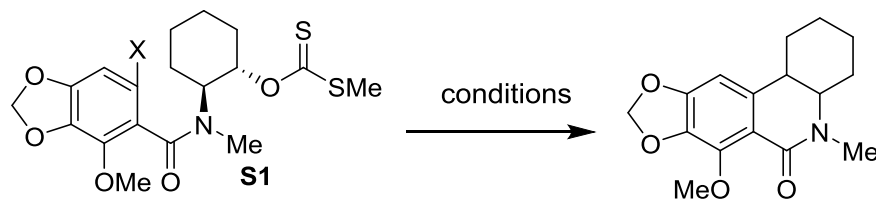
2013年に、Ragainsらはラジカル閉環反応を利用して(±)- $\gamma$ -lycoraneの合成<sup>1)</sup>を達成している(Scheme 2.1)。セレノエーテル**2-1**に対してベンゼン中でラジカル開始剤として広く用いられているAIBNと還元剤Tris(trimethylsilyl)silane (TTMSS)を加えて加熱条件下閉環反応を行うと、ラジカル中間体**2-2**を経由して閉環成績体**2-3**が44%収率で得られた。



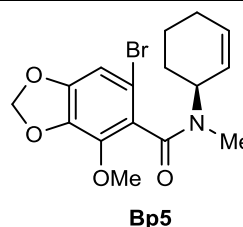
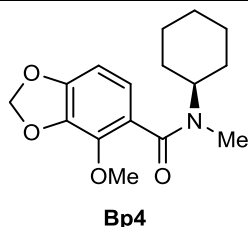
Scheme 2.1: Total synthesis of (±)- $\gamma$ -lycorane enabled by a radical cyclization reported by Ragains *et al*<sup>1)</sup>

今回、**S1a**、**S1b**を用いてラジカル環化反応を検討した(Table 2.1)。まずは**S1a**に対してAIBNと還元剤Bu<sub>3</sub>SnHを用い、トルエン中で加熱条件下閉環反応を検討したが目的の環化体ではなく副生成物**Bp4**が得られた(entry 1)。次に、*p*-キシレン中でマイクロ波(MW)を用いて180 °Cに加熱して反応させたところ副生成物**Bp4**が収率43%で得られた(entry 2)。還元反応を防ぐためビストリブチルスズ(Bu<sub>6</sub>Sn<sub>2</sub>)を用いトルエン中で加熱したものの反応は進行しなかった(entry 3)。AIBNを増量して*p*-キシレン中でMWを用いて180 °Cに加熱したものの反応は進行しなかった(entry 4)。Bu<sub>6</sub>Sn<sub>2</sub>ではなくTTMSSを用いて反応させた場合も還元体**Bp4**が得られた(entry 5)。**S1b**に対してトルエン中で加熱条件下閉環反応を検討したが反応は進行しなかった(entry 6)。*p*-キシレン中でMWを用いて180 °Cに加熱すると脱離体**Bp5**が得られた(entries 7 and 8)。副生成物**Bp4**と**Bp5**は<sup>1</sup>H NMR 芳香環プロトンの数とオレフィンピークおよびESI-MSで構造推定した。

**Table 2.1** Radical reaction with **S1**



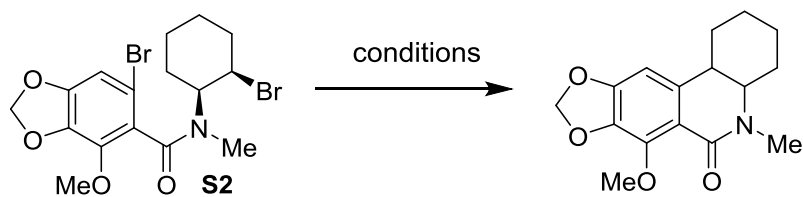
entry	S1	X	condition	result
1	<b>S1a</b>	X=H	AIBN 0.1 eq, Bu <sub>3</sub> SnH 1.2 eq, toluene (0.1 M), 80 °C, 3 h	<b>Bp4</b>
2	<b>S1a</b>	X=H	AIBN 0.4 eq, Bu <sub>3</sub> SnH 2.0 eq, <i>p</i> -xylene (0.02 M), MW, 180 °C, 5 min	<b>Bp4</b>
3	<b>S1a</b>	X=H	AIBN 0.2 eq, Bu <sub>6</sub> Sn <sub>2</sub> 1.2 eq, toluene (0.02 M), 80 °C, 4 h	0%
4	<b>S1a</b>	X=H	AIBN 1.2 eq, Bu <sub>6</sub> Sn <sub>2</sub> 1.2 eq, <i>p</i> -xylene (0.1 M), MW, 180 °C, 5 min	0%
5	<b>S1a</b>	X=H	AIBN 0.4 eq, TTMSS 2.0 eq, <i>p</i> -xylene (0.02 M), MW, 180 °C, 5 min	<b>Bp4</b>
6	<b>S1b</b>	X=Br	AIBN 0.1 eq, Bu <sub>3</sub> SnH 1.2 eq, toluene (0.1 M), 80 °C, 3 h	0%
7	<b>S1b</b>	X=Br	AIBN 0.4 eq, Bu <sub>3</sub> SnH 1.2 eq, <i>p</i> -xylene (0.02 M), MW, 180 °C, 5 min	<b>Bp5</b>
8	<b>S1b</b>	X=Br	AIBN 0.4 eq, Bu <sub>6</sub> Sn <sub>2</sub> 1.2 eq, <i>p</i> -xylene (0.1 M), MW, 180 °C, 5 min	<b>Bp5</b>



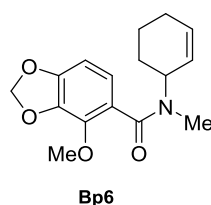
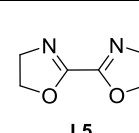
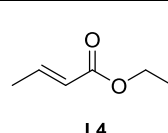
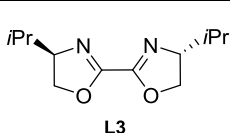
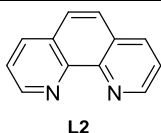
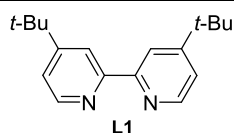
## 第2節 ニッケル触媒を用いる環化反応の検討

次に、**S2** を環化前駆体としニッケル触媒を用いた C–C カップリング反応を検討した (Table 2.2)。三種類のニッケル触媒を用いてそれぞれの反応条件を検討したが、**Bp6** と推定される副生成物が生じるものの所望の反応は進行しなかった。副生成物 **Bp4** と **Bp6** は <sup>1</sup>H NMR 芳香環プロトンの数とオレフィンピークおよび ESI-MS で構造推定した。

**Table 2.2** Nickel catalyzed C–C coupling reaction with **S2**.



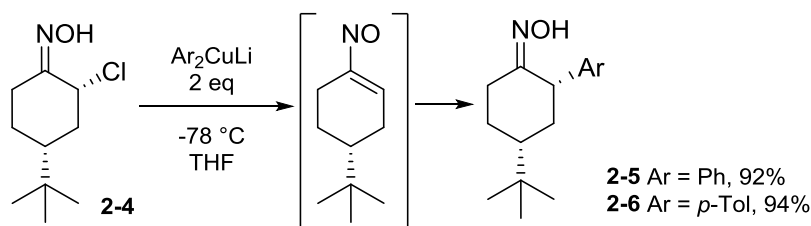
entry	Ni	ligand	reductant	additive	solvent	temperature	result
1	NiI <sub>2</sub> 10%	<b>L1</b> 10%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 to 90 °C	<b>Bp4, Bp6</b>
2	NiI <sub>2</sub> 10%	<b>L2</b> 10%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 to 90 °C	<b>Bp4, Bp6</b>
3	NiI <sub>2</sub> 10%	<b>L2</b> 10%	Mn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 to 90 °C	<b>Bp4, Bp6</b>
4	NiI <sub>2</sub> 10%	<b>L1</b> 10%	Zn 2 eq	Bu <sub>4</sub> NBF 1 eq, pyridine 1 eq	DMPU	80 °C	<b>Bp4, Bp6</b>
5	NiI <sub>2</sub> 10%	<b>L3</b> 10%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 to 90 °C	<b>Bp4, Bp6</b>
6	NiCl <sub>2</sub> 1 eq	<b>L4</b> 3 eq	Zn 3 eq	pyridine 1 eq	DMF	23 °C	<b>Bp4, Bp6</b>
7	NiCl <sub>2</sub> 1 eq	<b>L4</b> 3 eq	Mn 3 eq	pyridine 1 eq	DMF	23 °C	<b>Bp4, Bp6</b>
8	NiI <sub>2</sub> 10%	<b>L1</b> 10%	Mn 2 eq	pyridine 1 eq	DMPU	80 °C	<b>Bp4, Bp6</b>
9	NiI <sub>2</sub> 20%	<b>L2</b> 20%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 °C	<b>Bp4, Bp6</b>
10	NiI <sub>2</sub> 20%	<b>L3</b> 20%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 °C	<b>Bp4, Bp6</b>
11	NiCl <sub>2</sub> 20%	<b>L2</b> 20%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	23 °C	<b>Bp4, Bp6</b>
12	NiBr <sub>2</sub> 10%	<b>L2</b> 10%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	60 °C	<b>Bp4, Bp6</b>
13	NiBr <sub>2</sub> 10%	<b>L5</b> 10%	Zn 2 eq	pyridine 1 eq, MgCl <sub>2</sub> 1 eq	DMA	60 °C	<b>Bp4, Bp6</b>
14	NiBr <sub>2</sub> 10%	<b>L2</b> 10%	Zn 2 eq	pyridine 1 eq	DMA	60 °C	<b>Bp4, Bp6</b>
15	NiBr <sub>2</sub> 10%	<b>L5</b> 10%	Zn 2 eq	pyridine 1 eq	DMA	60 °C	<b>Bp4, Bp6</b>





### 第3節 分子間共役付加反応の検討

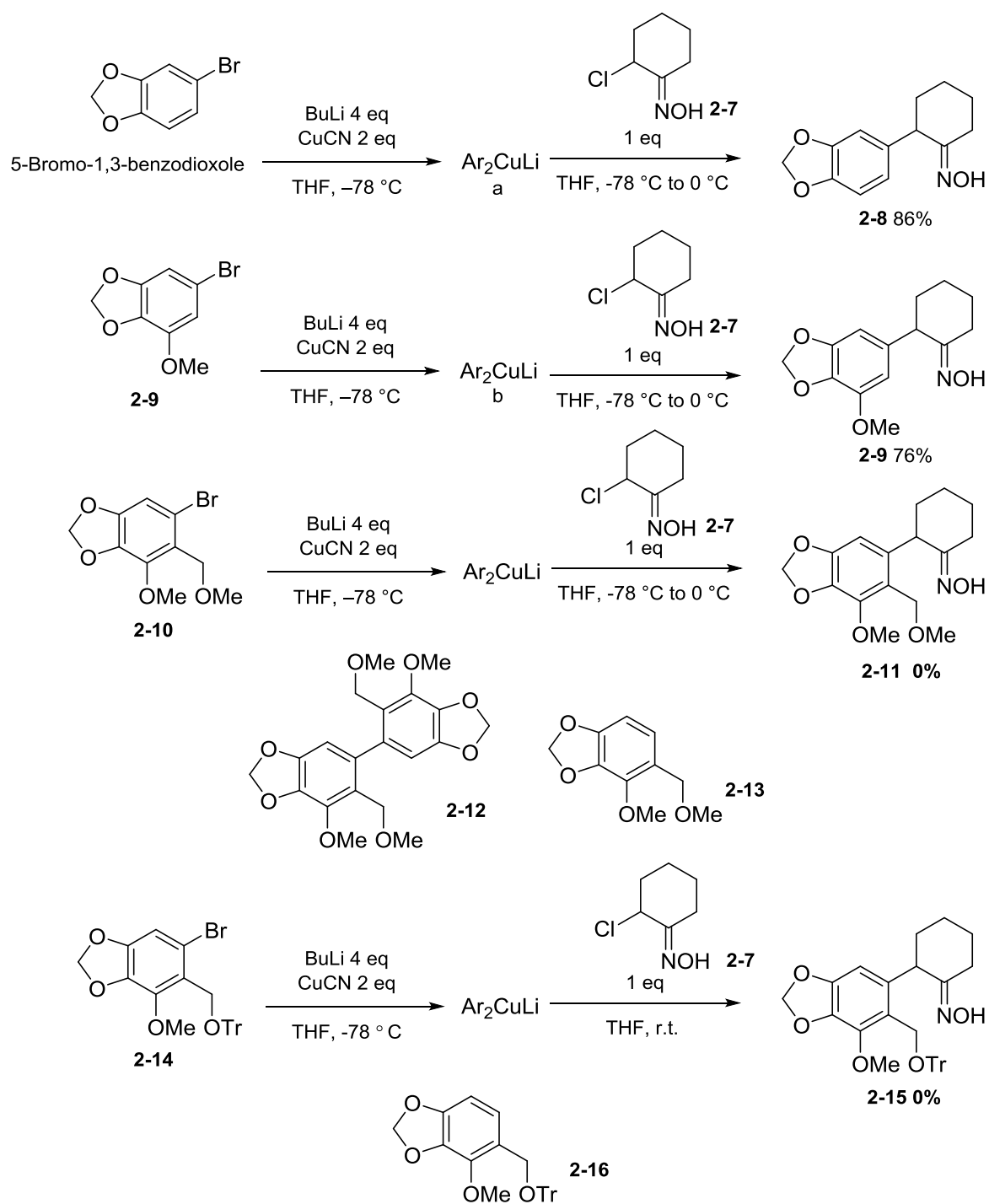
分子内 C-C カップリングによる閉環反応は困難であったので、分子間カップリング反応を検討することにした。分子間カップリング反応として  $\alpha$ -クロロオキシム **2-4** から系中で発生させたニトロソオレフィンと有機銅試薬の共役付加反応に着目した。Weinreb らは本反応を利用して  $\alpha$ -クロロオキシム **2-4** に対するアリール化反応に達成している (Scheme 2.3)<sup>2)</sup>。



Scheme 2.3 Examples of aryl cuprate conjugate addition reported by Weinreb<sup>2)</sup>

#### 3.1 モデル反応の検討

Weinreb らの報告を参考にして分子間カップリング反応を検討した (Scheme 2.4)。まずは 5-ブロモ-1,3-ベンゾジオキサールを THF 中でブチルリチウムと反応させてリチオ化した後、シアン化銅 (I) と反応させて有機銅試薬 **a** を生成した。続いて、**a** の THF 溶液中に  $\alpha$ -クロロオキシム **2-7** を加えたところ、目的物 **2-8** が 86% 収率で得られた。次に、より電子豊富な芳香環を持つ基質 **2-9** を用い有機銅試薬 **b** を調製して反応を行ったところ、所望の化合物 **2-9** が 76% 収率で得られた。しかしながら、メトキシメチル基を有する基質 **2-10** を用いる反応からは目的物 **2-11** は得られず二量体 **2-12** と還元体 **2-13** が生成した。有機銅試薬の集合体形成を抑制するため、嵩高いトリチロキシメチル基を有する基質 **2-14** を用いて反応を行ったものの目的物 **2-15** は得られず還元体 **2-16** が生成した。



**Scheme 2.4** Attempted conjugate additions with model substances.

### 3.2 基質合成

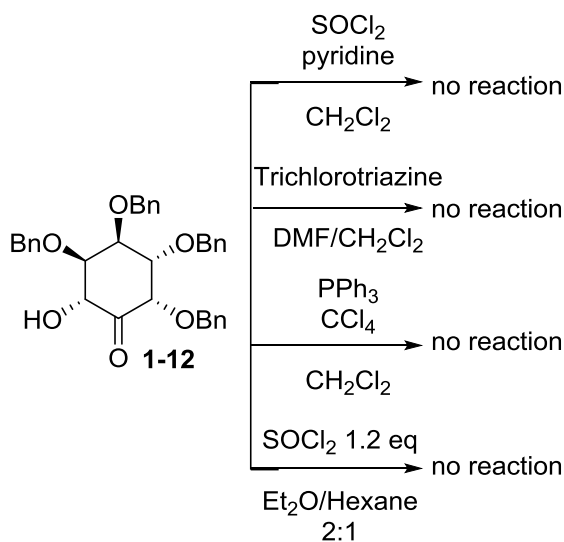
次にイノソース **1-12** を用いて基質となる  $\alpha$ -クロロオキシムの合成を試みた (**Scheme 2.5**)。まずイノソース **1-12** に対して塩化チオニルまたはトリクロロトリアゾールと反応させたが、反応は進行せず原料回収された。トリフェニルホスフィンと四塩化炭素を用いる Appel

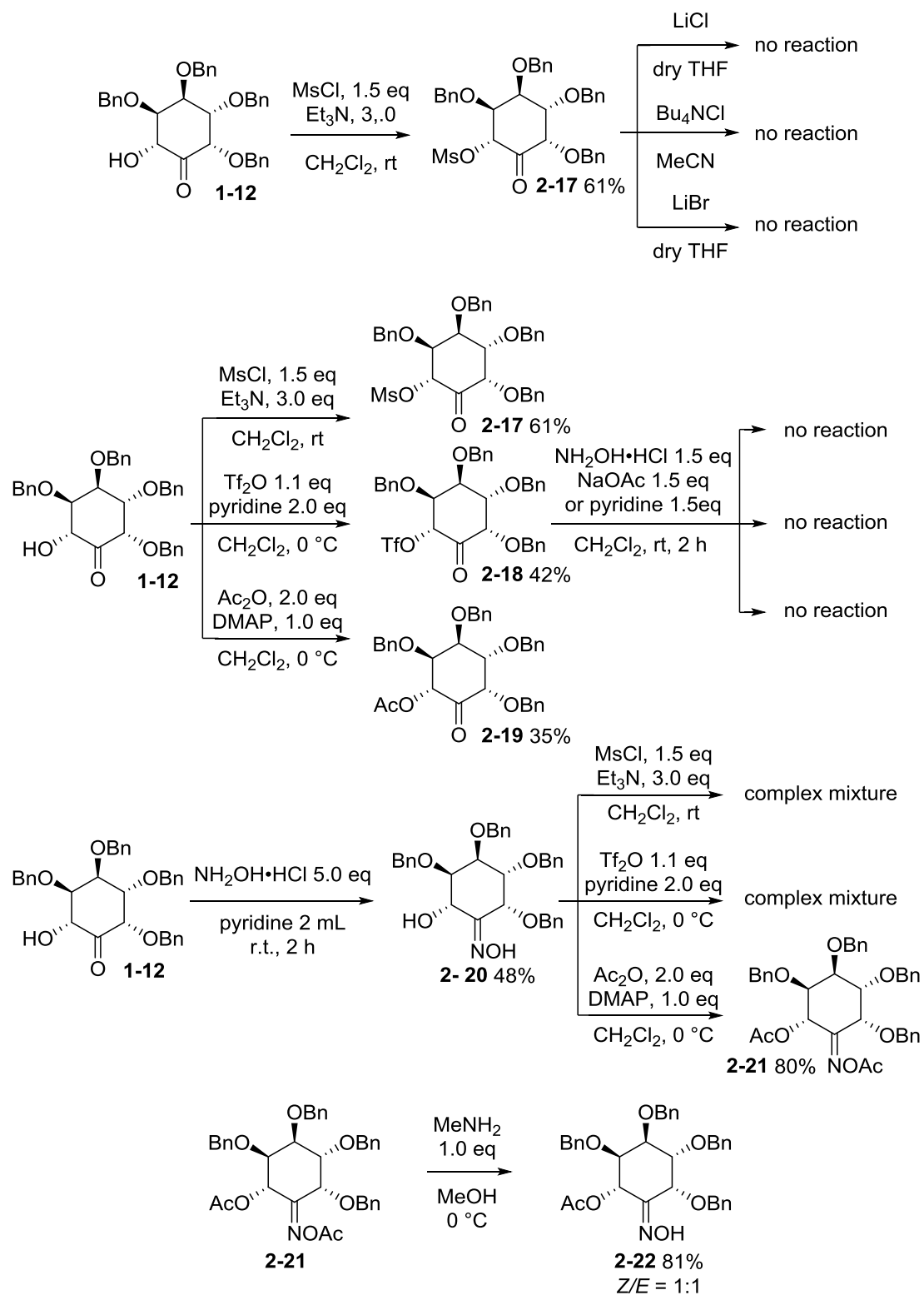
反応も進行せず原料回収された。エーテルとヘキサンの混合溶媒中で塩化チオニルを用いた  $S_Ni$  反応も試みたが進行せず原料回収された。

直接的な塩素原子導入は困難であったため、水酸基を脱離基に変換してから塩素原子への置換を試みた。メシル化は進行して **2-17** が得られた。THF 中で塩化リチウム、あるいはアセトニトリル中で塩化テトラブチルアンモニウムと反応させてみたが、反応は進行せず原料回収された。THF 中で臭化リチウムと反応させても反応は進行せず原料回収された。

ハロゲン原子の導入は困難であったため、オキシムの  $\alpha$  位にメシル基を導入した基質の合成を検討した。塩化メチレン中で **2-17** に対してヒドロキシルアミン塩酸塩とピリジンまたは酢酸ナトリウムを加えてオキシム化を試みたが、反応が進行しないまま原料回収された。次に、イノソース **1-12** に対してトリフラート化反応とアセチル化反応を行いトリフラート **2-18** とアセテート **2-19** を得た。トリフラート **2-18** とアセテート **2-19** のオキシム化を試みたが、これらの反応も進行せず原料回収された。

水酸基を修飾した後のオキシム化は困難だったので、先にオキシム化を行なった。イノソース **1-12** を用いてオキシム化反応を行うと、オキシム **2-20** が 48% 収率で得られた。**2-20** に対してトリフラート化反応とメシル化反応及びアセチル化反応を行ったところ、所望のトリフラートとメシラートは得られなかったものの、ジアセテート **2-21** が得られた。そこで **2-21** の選択的脱アセチル化を試みた。



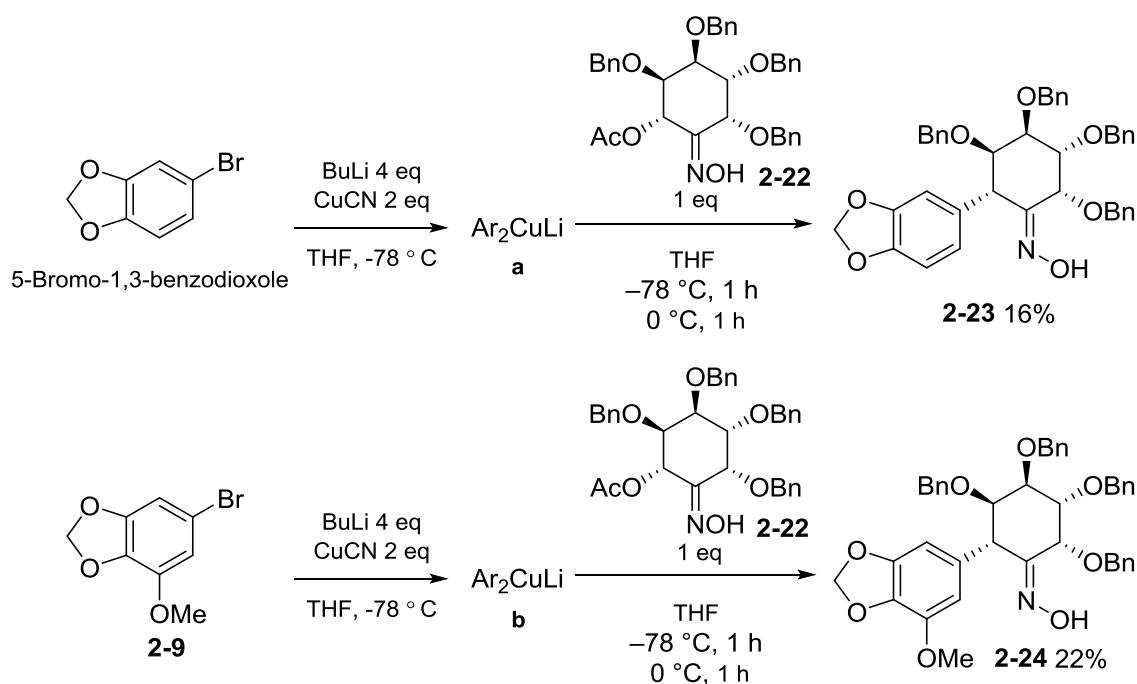


**Scheme 2.5** Synthesis of the substance for the key reaction.

**2-21** に対してメタノール中  $0^\circ\text{C}$  で 1 当量のメチルアミンを加えて反応させたところ、オキシムが選択的に脱アセチル化<sup>3)</sup>され、**2-22** が 81% 収率で得られた。

### 3.3 鍵反応の初期検討

基質が合成できたのでカップリング反応を行なった。ブロモベンゾジオキソールから調製した2当量の有機銅試薬 **a** に対して THF 中 $-78^{\circ}\text{C}$  で **2-22** を加えた後1時間反応させた<sup>8)</sup>と ころカップリング成績体 **2-23** を16%収率ながら得ることに成功した。また、メトキシ基を持つ臭化アリール **2-9** から調製した **b** を用いて反応を行うとカップリング成績体 **2-24** が22%収率で得られた (Scheme 2.6)。



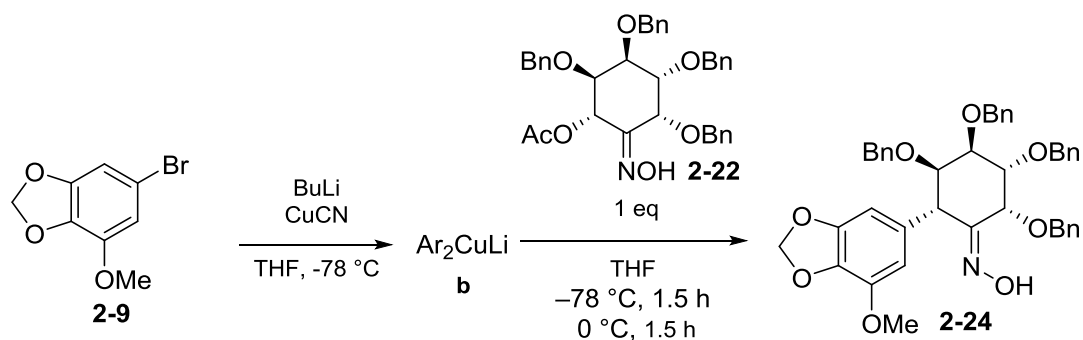
Scheme 2.6 Attempted key reaction.

### 3.4 反応条件の最適化

反応の収率を向上させるため、条件を検討した (Table 2.3)。オキシム **2-22** に対して3当量の有機銅試薬 **b** を使用して反応を行ったところ収率は25%に向上した (entry 2)。さらに、反応のスケールを2倍に上げて0.40 mmolのオキシム **2-22** を用いて反応を行ったところ収率は29%に向上した (entry 3)。次に、配位子添加の検討を行った。1,2-ジメトキシエタン (DME) とテトラメチルエチレンジアミン (TMEDA) は有機銅試薬の共役付加反応によく使われる配位子である。まず2.40 mmolの  $\text{BuLi}$  に対して1当量のDMEを用いて1.20 mmolの有機銅試薬 **b** を調製した後0.400 mmolのオキシム **2-22** を加えて反応させたところ収率は

45%に向上した (entry 4)。同じスケールで DME を TMEDA に変えて反応を行ったところ収率は 37%に低下した (entry 5)。トリフェニルホスフィン (PPh<sub>3</sub>) を配位子として加えて反応させたところ収率は 20%に低下した (entry 6)。スケールをさらに 0.60 mmol に上げても同程度の収率で目的物 **2-24** を得た (entry 7)。

**Table 2.3** Optimization of reaction conditions

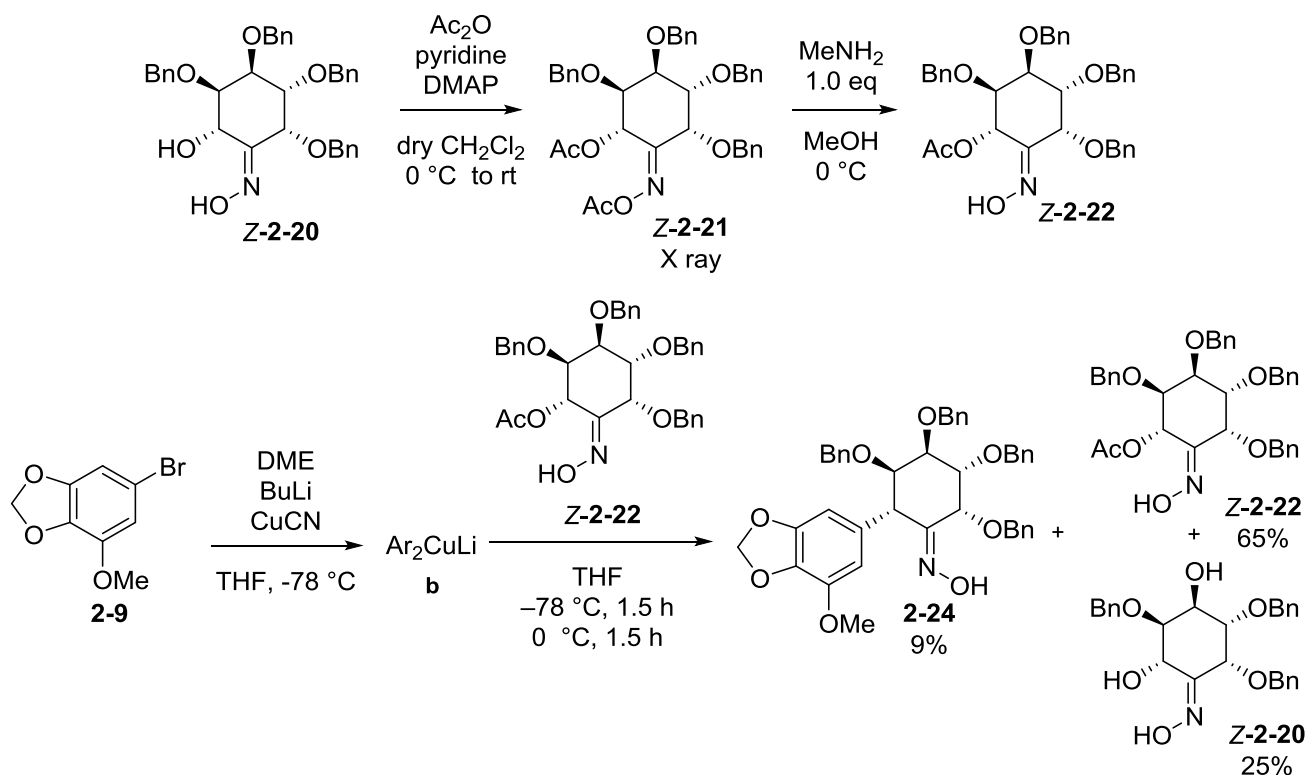


entry	oxime	Ar <sub>2</sub> CuLi	ligand (mmol)	yield
1	0.20 mmol	0.40 mmol	0	22%
2	0.20 mmol	0.60 mmol	0	25%
3	0.40 mmol	1.20 mmol	0	29%
4	0.40 mmol	1.20 mmol	DME 2.40	45%
5	0.40 mmol	1.20 mmol	TMEDA 2.40	37%
6	0.40 mmol	1.20 mmol	PPh <sub>3</sub> 1.2	20%
7	0.60 mmol	1.80 mmol	DME 3.60	43%

### 3.5 Z/E 異性体の反応性比較

以上の検討で反応収率はすべて 50%以下であった。副生成物を精査したところ、 $\alpha$ -ヒドロキシオキシムが 30%程度生成していることが分かった。反応に用いたオキシムの E/Z 異性体比は 1:1 であったが、生成した  $\alpha$ -ヒドロキシオキシムは単一の異性体だった。この結果から片方の異性体はニトロソオレフィンへと変換していないのではないかと考えた。生成した

$\alpha$ -ヒドロキシオキシムを用いてジアセトキシオキシムを合成し X 線結晶構造解析で構造決定した結果、生成物のオキシムは Z 体であることが分かった。続いて、ジアセトキシオキシムに対して選択的脱アセチルを行い Z 体の  $\alpha$ -アセトキシオキシムを合成した。Z 体の  $\alpha$ -アセトキシオキシムを用いて共役付加反応を行ったところ、目的のカップリング成績体が 9% 収率で得られて原料が 65%回収されて  $\alpha$ -ヒドロキシオキシムが 25%収率で生成した。この結果から、予想通り Z 体は反応しにくいことが確認された (Scheme 2.7)。



**Scheme 2.7** Synthesis of Z-configured oxime and its conjugate addition reaction.

### 3.6 溶媒の検討

反応溶媒をジエチルエーテルやトルエンに変換してそれぞれ反応を検討した (Table 2.4)。いずれも収率低下する結果となった。ジエチルエーテルを溶媒に用いた場合、目的物 **2-22** が 22% 収率で得られた (entry 2)。トルエンを用いた場合では、有機銅試薬の溶解性が悪くて、目的物が 24% 収率で得られた (entry 3)。

**Table 2.4** Screening of solvents.

entry	solvent	yield
1	THF	45%
2	Et <sub>2</sub> O	22%
3	Toluene	24%

### 3.7 銅塩の検討

銅塩としてチオフェン-2-カルボン酸銅や酢酸銅を用いる反応を試みた (**Table 2.5**)。いずれも収率が低下する結果となった。チオフェン-2-カルボン酸銅を用いた場合、目的物 **58** が 28%収率で得られた (entry 2)。酢酸銅を用いた場合では、収率はさらに 13%まで低下した (entry 3)。

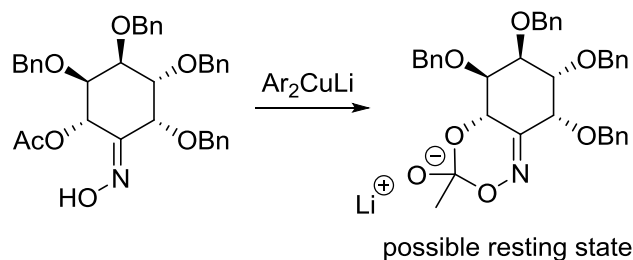
**Table 2.5** Screening of Cu<sup>I</sup> salts.

entry	solvent	yield
1	CuCN	45%
2	CuTc	28%
3	CuAc	13%

### 3.8 基質の脱離基の検討

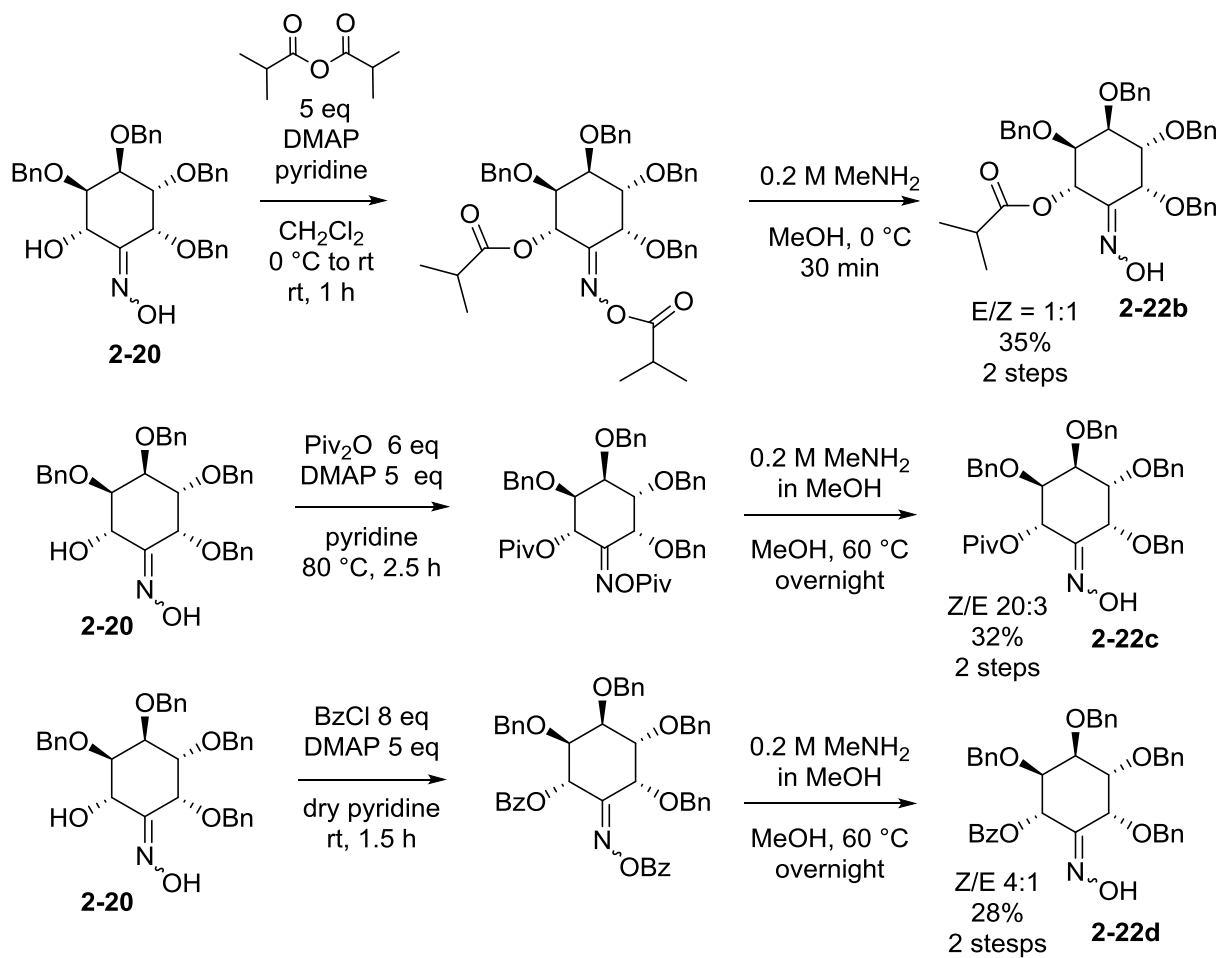
1,4-付加反応の収率が 50%を超えないことと基質の Z 体異性体の反応性が低いことから Z 体異性体が反応する際に **Figure 2.2** に示す休眠状態が形成していることを推測した。基質の脱離基を嵩高くすればこの休眠状態の形成を抑制できるのではないかと考えたので、脱離基を嵩高いものに変換した基質を合成して 1,4-付加を検討することとした。





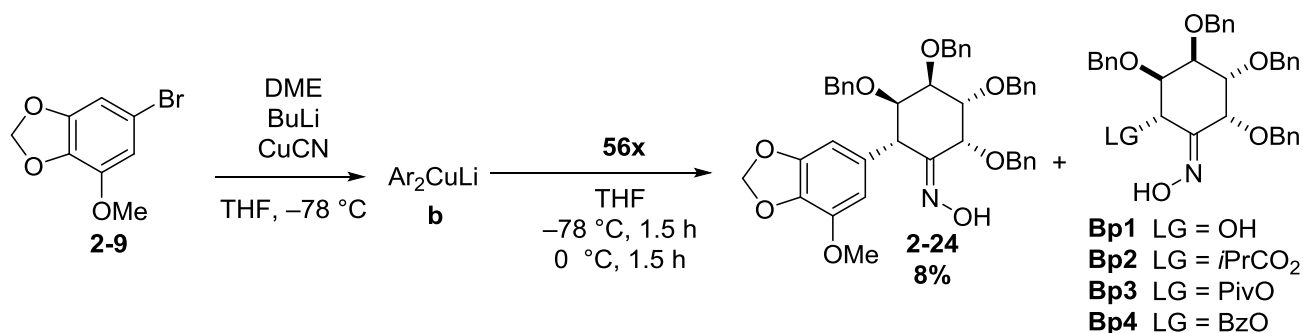
**Figure 2.2** Proposed possible resting state.

**Scheme 2.8** に示すように **2-22b**、**2-22c**、**2-22d** 三つの基質を合成した。それぞれを用いて 1,4-付加反応を行った (**Table 2.6**)。脱離基はアセチル基をイソブチリル基に変換した **2-22b** ( $Z/E = 1:1$ )を用いた場合で、目的物の収率が 25%まで低下し、副生成物は **Bp1** 15%、**Bp2** 30%それぞれ回収された (entry 2)。アセチル基をさらに嵩高くしてピバロイル基とした **2-22c** ( $Z/E = 2:1$ )を用いると、目的物が 26%収率で得られ、副生成物は **Bp3** のみ 52%回収された (entry 3)。脱離基をベンゾイル基とした **2-22d** ( $Z/E = 4:1$ )を用いた場合では、目的物の収率がさらに 15%まで低下し、副生成物は **Bp4** のみ 39%回収された (entry 4)。以上の結果から、脱離基を嵩高くすると、1,4-付加は進行しにくくなることが分かった。そこで、立体障害のため反応速度が遅くなったと考えて反応時間を延長して反応させようとした。**2-22c** ( $Z/E = 20:3$ )を用いて $-78\text{ }^{\circ}\text{C}$ で 1.5 時間、 $0\text{ }^{\circ}\text{C}$ で 1.5 時間反応させたのち、室温に室温して 18 時間されたところ、目的物の収率は 26%から 38%に向上した (entry 5)。回収された **Bp3** を用いて単一の  $Z$  異性体を合成して同じように反応を行ったところ、収率はさらに 42%まで向上した (entry 6)。基質 **2-22c** を用いて反応時間を延長することで収率が向上することが分かった。次に最も収率の高い基質 **2-22** に戻して同じよう反応時間を延長して反応させたところ、逆に収率が低下する結果が得られた (entry 7, 8)。



**Scheme 2.8** Syntheses of substrates.

**Table 2.6** 1,4-addition using substitutes with different leaving groups.

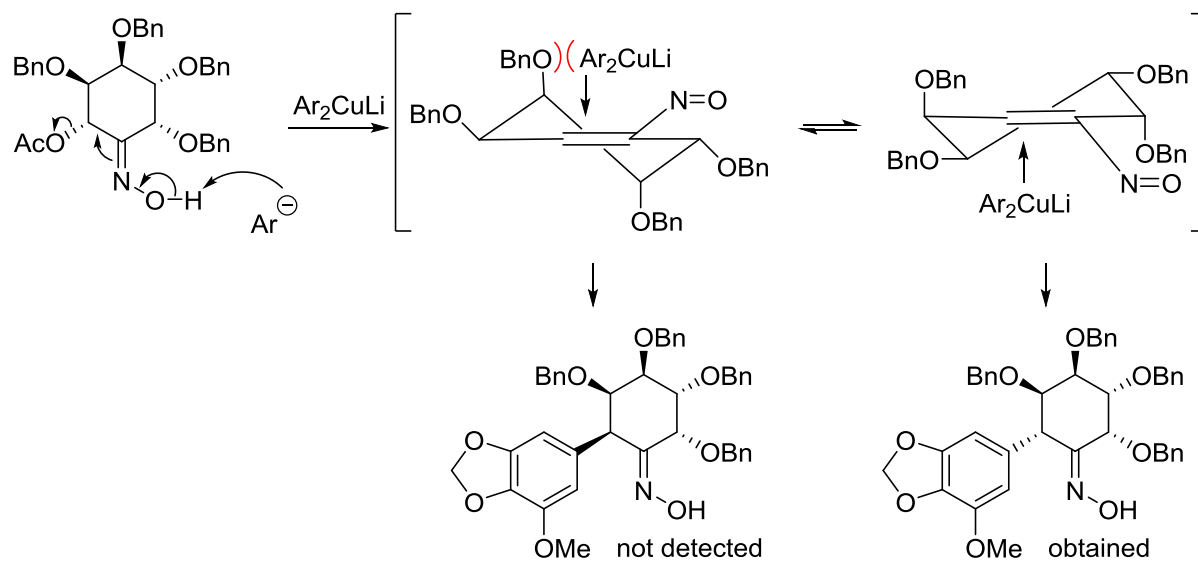


entry	substitute	Z/E	TM yield	recovery
1	<b>2-22</b>	1/1	45%	<b>Bp1</b> 30%
2	<b>2-22b</b>	1/1	25%	<b>Bp1</b> 15% <b>Bp2</b> 30%
3	<b>2-22c</b>	2/1	26%	<b>Bp3</b> 52%
4	<b>2-22d</b>	4/1	15%	<b>Bp4</b> 39%
5 <sup>a)</sup>	<b>2-22c</b>	20/3	38%	<b>Bp1</b> 16% <b>Bp3</b> 9%
6 <sup>a)</sup>	<b>2-22c</b>	1/0	42%	<b>Bp1</b> 13% <b>Bp3</b> 11%
7 <sup>a)</sup>	<b>2-22</b>	1/1	26%	<b>Bp4</b> 48%
8 <sup>a)</sup>	<b>2-22</b>	5/1	8%	<b>Bp4</b> 49%

a) stirred for 18 h at room temperature after stirring at 0 °C for 1.5 h .

### 3.9 ジアステレオ選択性の考察

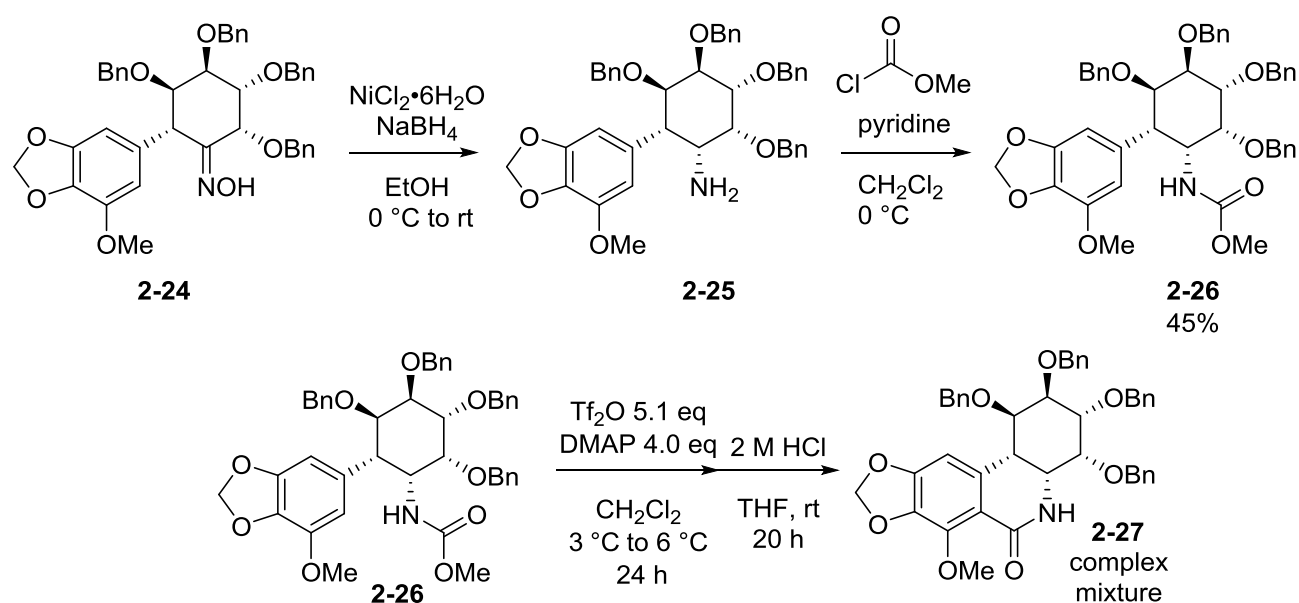
アリール化の立体選択性は **Scheme 2.9** に示すように説明できる。まず、キュプラートがオキシムの水酸基を脱プロトン化するとアセテートが脱離してニトロソオレフィンが生じる。キュプラートの共役付加はねじれ歪みが小さくなる *axial* 側から進行する。ニトロソオレフィンの2つのコンフォメーションのうち左のコンフォメーションでは図に示すベンジルオキシ基による立体障害があるため、右のコンフォメーションから優先して付加が進行し、*trans* 体が選択的に生成する。



**Scheme 2.9** Rational for Diastereoselective Arylation

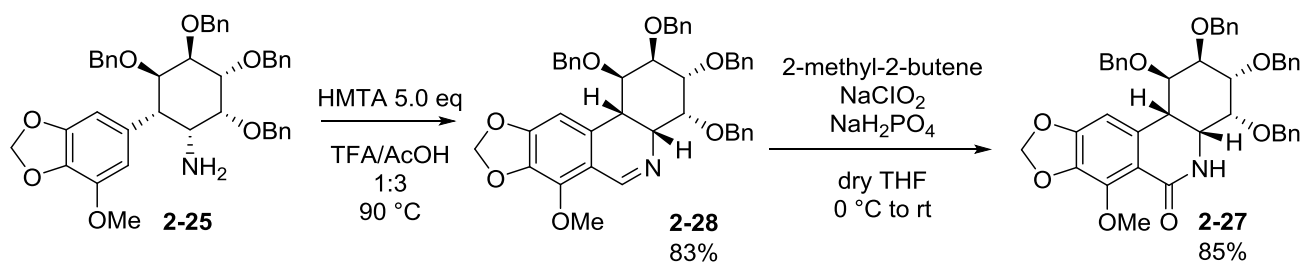
## 第4節 ラクタム環閉環

カップリング成績体 **2-24** が得られたので、続いてラクタム環閉環を行った (**Scheme 2.10**)。まず Bischler–Napieralski 反応<sup>4)</sup>を検討した。**2-24** に対して触媒量の  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  の存在下で  $\text{NaBH}_4$  を加えて還元反応を行いアミン **2-25** を得た。クロロギ酸メチルと反応させるとカルバメート **2-26** が 45% 収率で得られた。Bischler–Napieralski 反応を行ったところ、複雑な混合物が得られた。



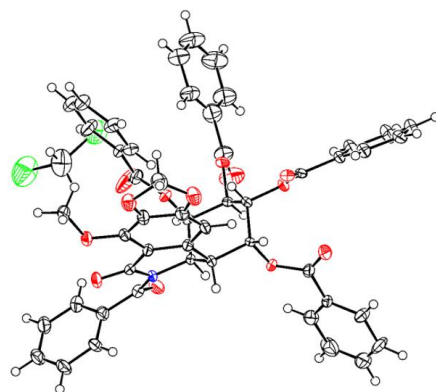
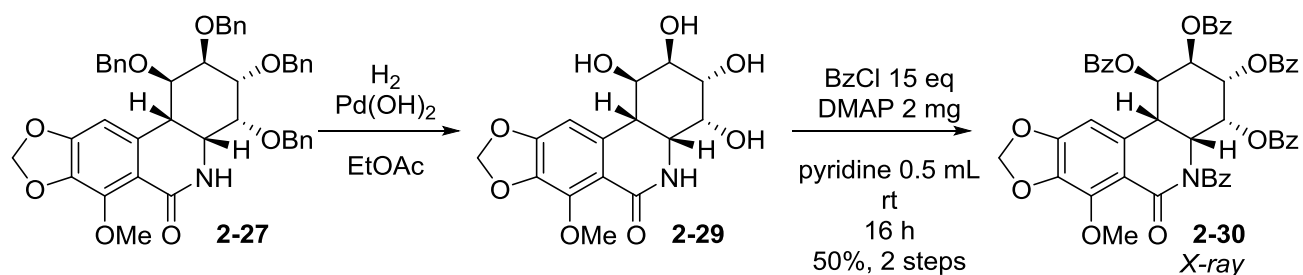
**Scheme 2.10** Attempted formation of the lactam ring via Bischler–Napieralski reaction.

次に還元反応で得られたアミン **2-25** を用いて位置選択的なホルミル化に続くイミノ化反応<sup>5)</sup>を検討した (**Scheme 2.11**)。アミン **2-25** に対して TFA/AcOH (3:1) の混合酸性溶媒中でヘキサメチレンテトラミン (HMTA) と反応させるとイミン **2-28** が得られた。所属する研究室で開発された Pinnick 酸化<sup>6)</sup>を用いるアミドへの変換を行ったところ、ラクタム **2-27** を良好な収率で得ることに成功した。



**Scheme 2.11** Formation of the lactam ring.

構造決定のために **2-27** に対して水酸化パラジウム触媒を用いてベンジル基を除去した後にベンゾイル基で保護したところ結晶性の良い **2-30** が得られた。X 線結晶構造解析によって絶対立体配置も含めて構造を確認した (**Scheme 2.12**)。



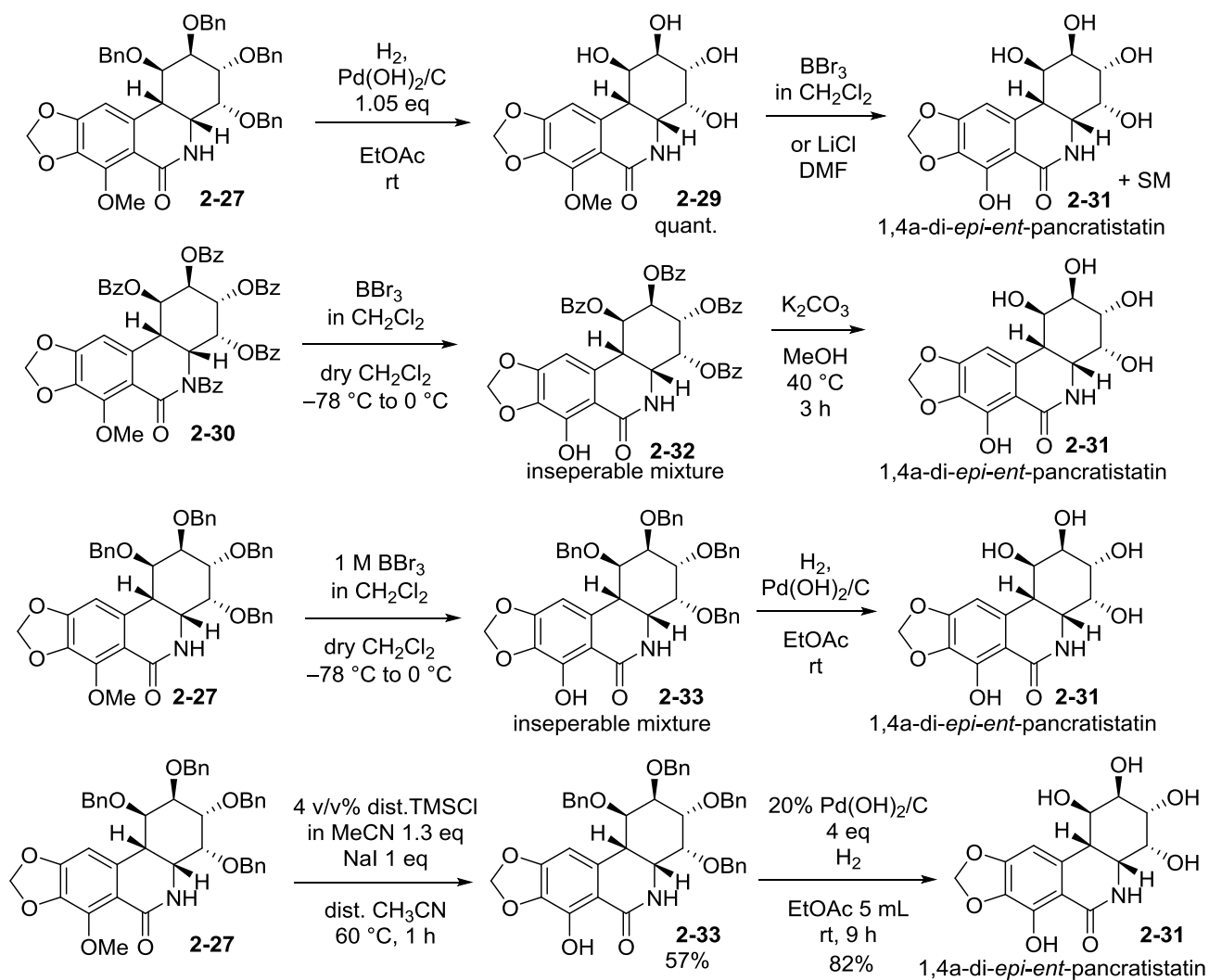
ORTEP of **2-30** (50% probability)

**Scheme 2.12**

## 第 5 節 脱保護の条件検討

二種類の保護基はメチル基とベンジル基を脱保護する順序を検討した (Scheme 2.13)。まず **2-27** に対して 1.05 当量の水酸化パラジウム触媒の存在下で水添反応を行うと、脱ベンジルした **2-31** が定量的に得られた。次に三臭化ホウ素 ( $\text{BBr}_3$ ) を用いて脱メチルを行ったところ、**2-31** の溶解性が低いためか、目的物は生成するものの **2-30** が完全に消失せず回収された。DMF 中で塩化リチウム ( $\text{LiCl}$ ) を用いる脱メチルも検討したが、反応が進行せずに原料回収された。また、構造決定する際に合成した **2-30** に対しても脱保護を検討した。**2-30** に対して  $\text{BBr}_3$  のジクロロメタン溶液と反応させたところ、メチル基が完全に除去されてベンゾイル基もいくつか除去されたものの混合物が得られた。この混合物に対して、MeOH 中  $40^\circ\text{C}$  で炭酸カリウムと反応させると目的の *pancratistatin* 立体異性体 *1,4a-di-epi-ent-pancratistatin* (**2-31**) が生成したものの、精製は困難であった。

次に先に脱メチル化するルートを検討した。**2-27** に対して  $\text{BBr}_3$  のジクロロメタン溶液と反応させたところ、ベンジル基もいくつか除去されたものとメチルが除去されていないものの混合物が得られた。**2-27** に対して  $\text{TMSCl}$  と  $\text{NaI}$  を 1 当量ずつ加えて  $60^\circ\text{C}$  で反応を行うと、脱メチル化した **2-33** が 57% 収率で得られた。さらに加水素分解条件<sup>7)</sup>で脱ベンジル化したところ、目的の *pancratistatin* 立体異性体 *1,4a-di-epi-ent-pancratistatin* (**2-31**) が 82% 収率で得られた。



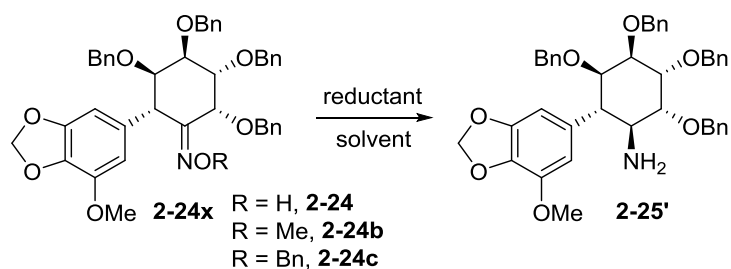
**Scheme 2.13** Deprotection.



## 第6節 オキシムのトランス還元条件検討

オキシム **2-24** のトランス還元条件検討を行った。まずオキシムの無保護状態でトランス還元条件を検討した (Table 2.7)。Entry 1 と entry 2 ではアミンとボランの錯体を還元剤として反応させたところ、どちらも反応せずに原料回収された。LiAlH<sub>4</sub> で還元を行った場合には、*cis*-アミン **2-25** が 37% 収率で得られたが、*trans*-アミン **2-25'** は生成しなかった (entry 3)。水酸化パラジウム触媒の存在下で水添反応を行うと、ベンジル基が除去されたシスアミン **2-25** が得られた (entry 4)。金属亜鉛を還元剤に用いた場合には、反応を進行せず原料回収された (entry 5)。SmI<sub>2</sub> を用いた場合には、*cis*-アミン **2-25** が 19% 収率で得られた (entry 6)。Entry 7 と entry 8 ではメチル化したオキシム **2-25b** の還元反応を検討した。Me<sub>4</sub>N(AcO)<sub>3</sub>BH を用いた場合でやはり反応は進行しなかった (entry 7)。奈良坂らの立体選択的還元法<sup>8)</sup>を用いると、構造不明な副生成物が生成し目的の *trans*-アミン **2-25'** はやはり得られなかった (entry 8)。メチル基をベンジル基に変換して奈良坂らの還元法を用いると、反応は進行せずに原料回収された (entry 9)。ボランの THF 錯体を還元剤に用いても反応しなかった (entry 10)。

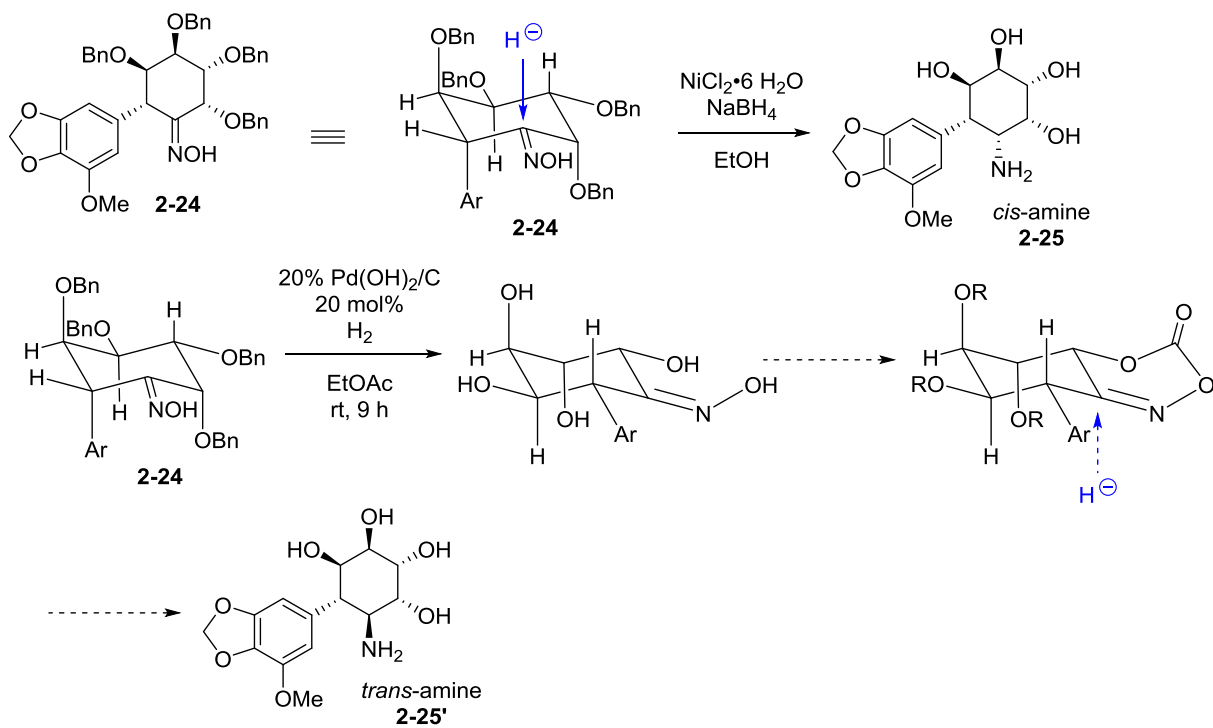
**Table 2.7** *Trans*-selective reduction of Oxime **58x**



entry	R	reductant	solvent	result
1	H	$\text{Me}_4\text{N}(\text{AcO})_3\text{BH}$	AcOH/MeCN	no reaction
2	H	$t\text{BuNH}_2 \cdot \text{BH}_3$	toluene	no reaction
3	H	$\text{LiAlH}_4$	THF	<i>cis</i> 37%
4	H	$\text{Pd}(\text{OH})_2, \text{H}_2$	EtOAc	<i>cis</i> <sup>a)</sup>
5	H	Zn	AcOH	no reaction
6	H	$\text{SmI}_2$	THF	<i>cis</i> 19%
7	Me	$\text{Me}_4\text{N}(\text{AcO})_3\text{BH}$	AcOH/MeCN	no reaction
8	Me	NaOMe, $\text{LiAlH}_4$	THF	unknown Bp
9	Bn	NaOMe, $\text{LiAlH}_4$	THF	no reaction
10	Bn	$\text{BH}_3 \cdot \text{THF}$	THF	no reaction

a) *cis*-amine with 4 hydroxy groups deprotected.

以上の条件検討でトランス還元は成功していない理由はオキシム近傍に存在するアリール基とベンジルオキシ基が両方ともアキシアル位に配置されているため、ヒドリドが反対側から付加するからだと考えた。そして、**Scheme 2.14** に示す戦略を計画した。オキシム **2-24** を触媒量の水酸化パラジウムを用いた水添反応で選択的にベンジル基を除去することでオキシムのコンフォメーションをフリップさせた後、6員環形成によってコンフォメーションを固定した状態で還元すれば *trans*-アミンが得られると期待した。残念ながら、種々条件検討したが、目的の6員環中間体が得られなかったため、この戦略も奏効しなかった。



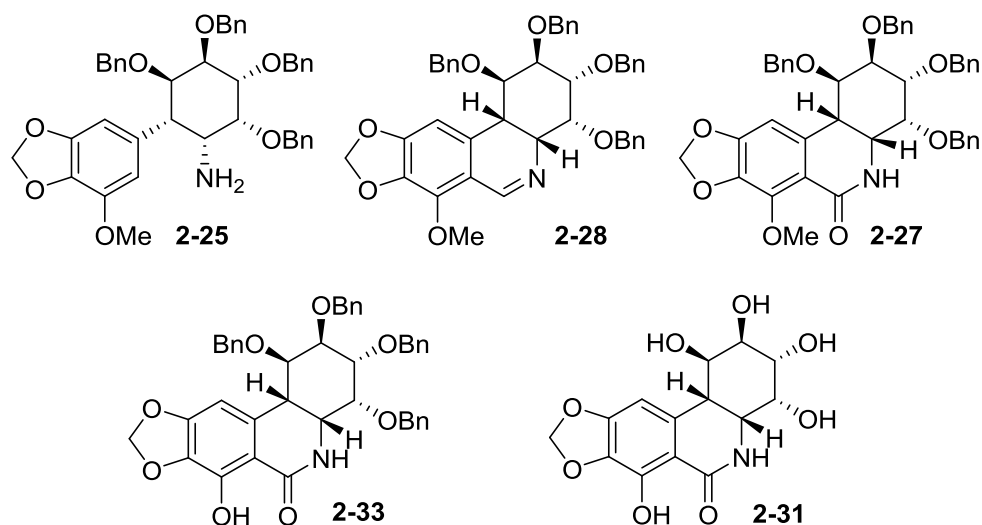
**Scheme 2.14** Strategy for *trans*-selective reduction of oxime **2-24**.

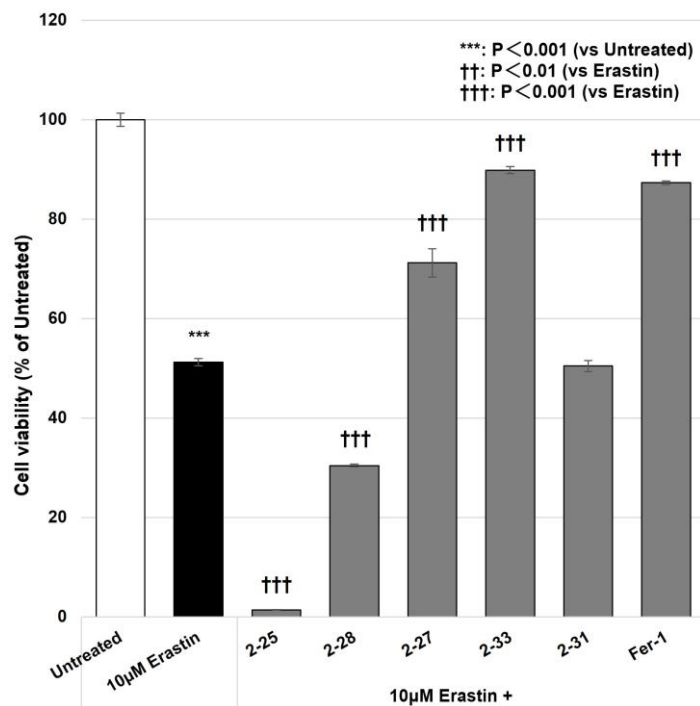
## 第7節 活性評価

Pancreatistatin は優れた抗腫瘍活性を持つことは第1章第1節に紹介した。

今回、初めに *in vitro* でヒト乳がん細胞 MCF7、ヒト膵癌細胞 MiaPaca2 及び PANC-1、それぞれに対して本研究で合成した 1,4a-di-*epi-ent-pancratistatin* 及びその合成中間体の細胞増殖抑制効果を評価したが、0.03  $\mu\text{M}$ ~3  $\mu\text{M}$  の濃度範囲ではいずれの化合物でも有意な効果が見られなかった。

次に、フェロトーシス抑制活性に注目した。フェロトーシス（鉄依存性細胞死）は2012年に Dixon らによって新しく報告された細胞死機構であり、細胞内自由鉄 ( $\text{Fe}^{2+}$ ) を触媒として細胞膜リン脂質の過酸化反応が連鎖し脂質ヒドロキシラジカルが蓄積することで細胞が死に至ると考えられている。心臓や腎臓の虚血再灌流障害や脳卒中などの虚血性疾患と ALS、パーキンソン病、アルツハイマー病、ハンチントン舞踏病などの神経変性疾患などにおいて、フェロトーシスが関与することが報告されている<sup>12)</sup>。今回、ヒト肝がん細胞株 Hep3B に対するフェロトーシス抑制活性を評価した (Figure 3)。その結果、化合物 2-24、2-27、2-33 はフェロトーシス抑制活性を示した。特に 2-33 はフェロトーシス阻害剤である Ferrostatin-1 よりも少し強い活性を持つことが明らかになった。一方で、化合物 2-25、2-28 は Hep3B 細胞に対して細胞毒性を示した。最終生成物すなわちすべての水酸基が脱保護された 1,4a-di-*epi-ent-pancratistatin* 2-31 は Hep3B 細胞にほぼ影響がないことが分かった。以上の結果によって、活性のある化合物の酸素上の置換基が活性の発現に重要であることが示唆されている。





**Figure 4.** Anti-ferroptosis activity of compounds on erastin-treated hepatoma Hep3B cells at 10 µM.

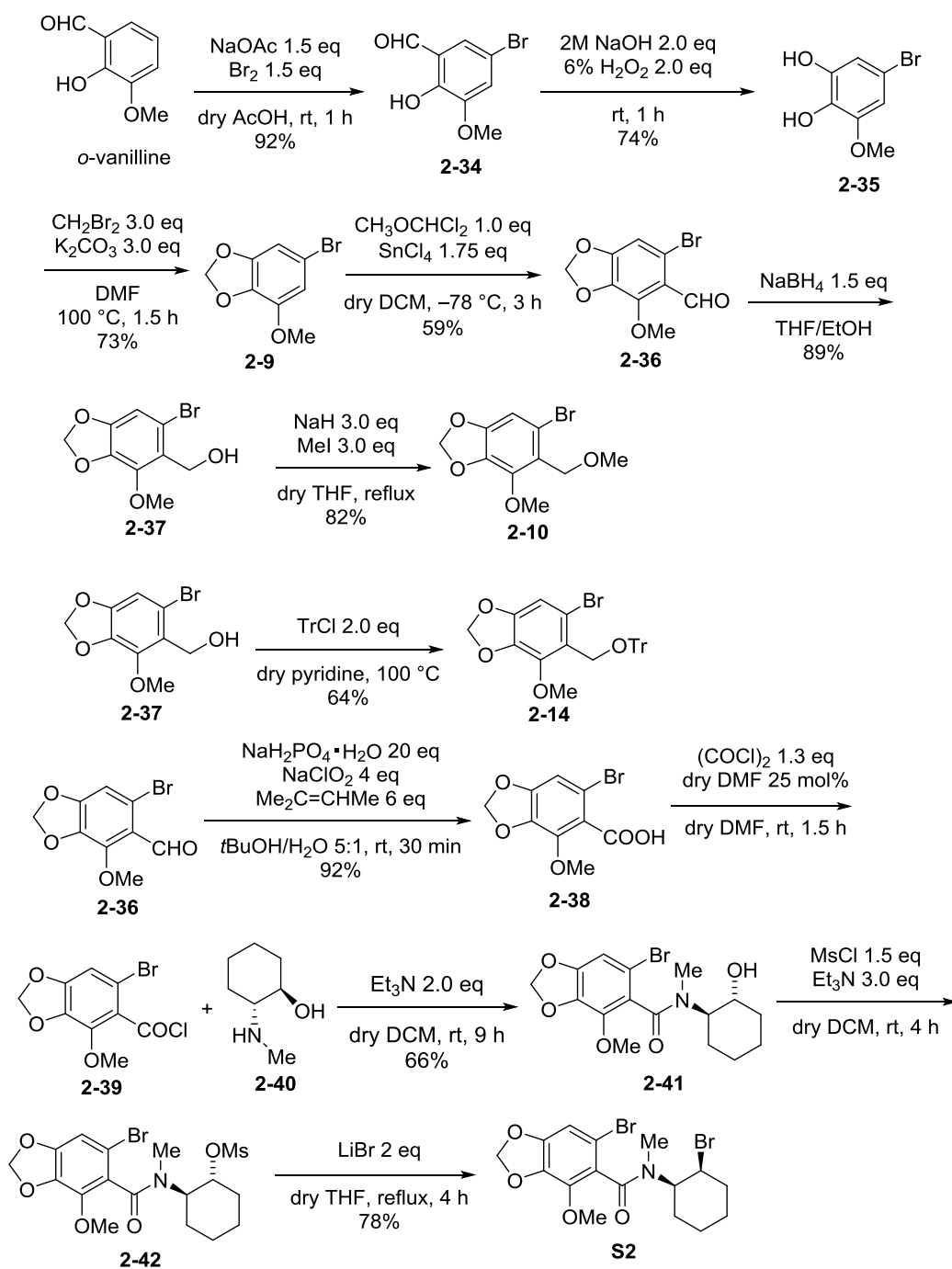
Fer-1: ferrostatin-1.

## 第 8 節 基質合成

### 8.1 芳香環ユニットの合成

アリールキュープラートの前駆体として用いた臭化アリールは以下のように合成した (Scheme 2.17)。o-vanillin をブロモ化した後、Dakin 酸化<sup>13)</sup>によりカテコール **2-35** を得た。カテコール部位をメチレンジオキシ化<sup>14)</sup>した後、ジクロロメチルメチルエーテルと塩化スズ (IV) を用いホルミル基を導入し **2-36** を得た<sup>15)</sup>。水素化ホウ素ナトリウムを用いホルミル基を還元しアルコール **2-37**<sup>16)</sup>を合成した。**2-37** の水酸基をメチル化<sup>17)</sup>あるいはトリチル化<sup>16)</sup>して **2-10** と **2-14** を得た。

**2-36** のホルミル基をカルボキシ基へと酸化<sup>17)</sup>し、市販のエポキシシクロヘキサンから合成<sup>18)</sup>したアミノアルコール **2-40** と縮合<sup>19)</sup>することで所望の 2-ヒドロキシアミド **2-41** を合成した。次に、得られた化合物 **2-41** のヒドロキシ基を塩化メシルで活性化した後にブロモ化体 **S2** が得られた。

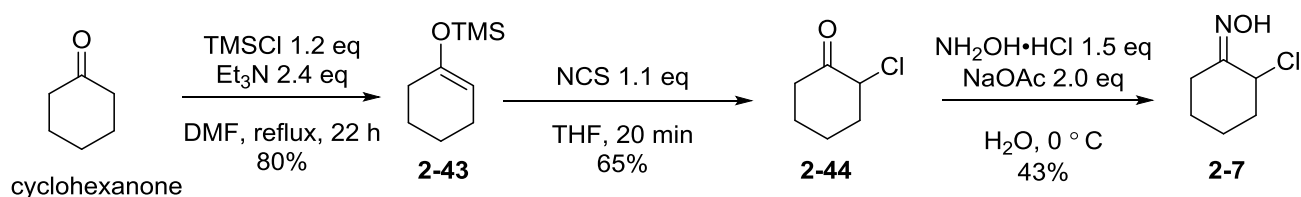


**Scheme 2.17** Synthesis of Arylbromide substrates.

## 8.2 オキシムの合成

$\alpha$ -クロロオキシム **2-7**<sup>20)</sup>は以下のように合成した (**Scheme 2.18**)。シクロヘキサノンと塩化トリメチルシリル (TMSCl) を DMF 中でトリエチルアミンの存在下反応させるとエノールエーテル **2-43** が得られた。*N*-クロロスクシンイミド (NCS) を用いて塩素化すると  $\alpha$ -クロ

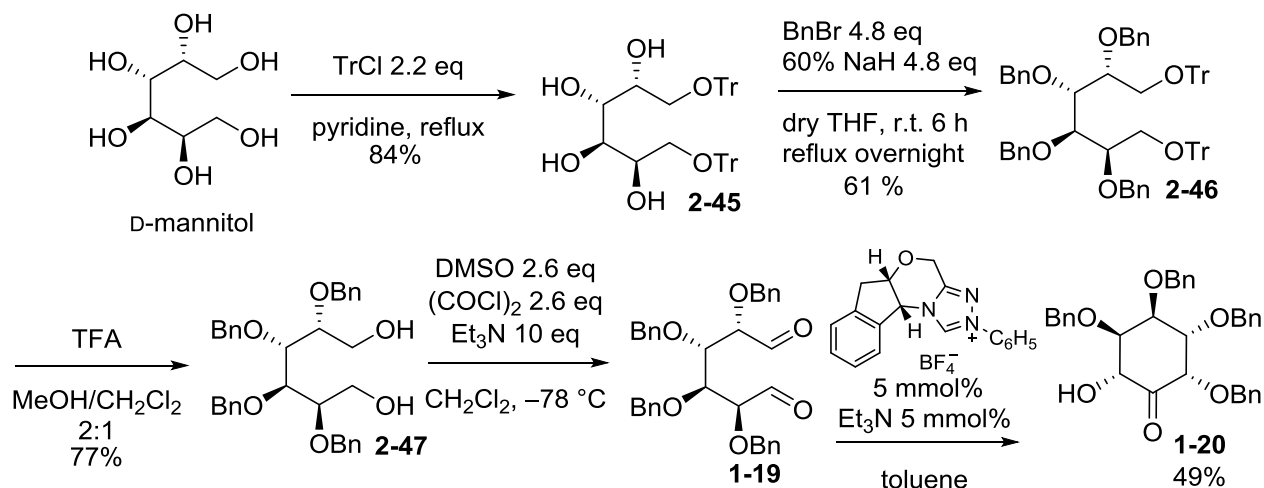
ロケトン **2-44** が得られた。水中で酢酸ナトリウムの存在下ヒドロキシルアミン塩酸塩を加えて反応させると  $\alpha$ -クロロオキシム **2-7** が得られた。



**Scheme 2.18** Synthesis of oxime **42**.

### 8.3 イノソースの合成

イノソース **1-20** は以下のように合成した<sup>21)</sup> (**Scheme 2.19**)。まず、塩化トリチルで D-mannitol の二つの第一級ヒドロキシ基を保護して化合物 **2-45** を得た。次に、臭化ベンジルで残った4つのヒドロキシ基を保護して化合物 **2-46** を合成した。その後、TFA を用いてトリチル基を除去したところ、ジオール **2-47** が得られた。ジオール **2-47** に対し Swern 酸化を行うとジアルドース **1-19** が得られた。最後に NHC 触媒を用いたベンゾイン型環化反応を行ったところ、イノソース **1-20** が 49% 収率で得られた。



**Scheme 2.19** Synthesis of Inosose **1-20**.

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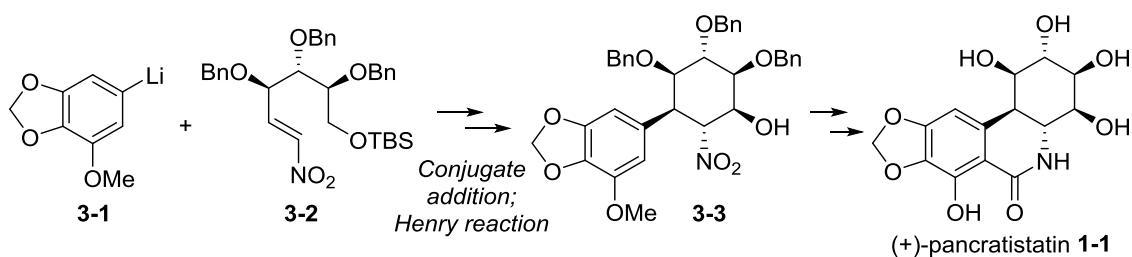
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### 第 3 章

## **Pancratistatin** 三環性骨格 **hexahydrophenanthridinone** の 新規一般合成法の確立





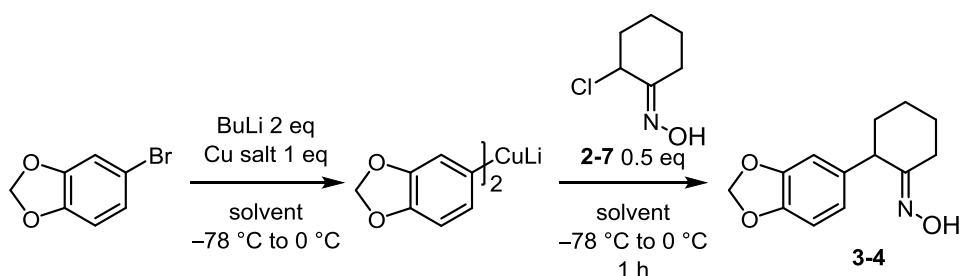
**Scheme 3.1** Total synthesis of pancratistatin reported by Liu *et al.*

第2章 1,4a-di-*epi-ent*-pancratistatin の全合成によって新たな hexahydrophenanthridinone 三環性骨格構築法を開発した。その有用性を示すために、更なる反応の最適化と適用範囲の調査を行った。

## 第2節 有機銅試薬による共役付加反応の条件検討

2-7 (*E* 体のみ) を基質に用いて共役付加の反応条件を検討した (Table 3.1)。4 種の銅塩を用いてそれぞれ反応を検討した (entry 1~4) ところ、Copper(I) thiophene-2-carboxylate (CuTc) を用いた場合に最も良い結果が得られ、目的物 3-4 (*E* 体のみ) が 85% 収率で得られた。次に、溶媒に Et<sub>2</sub>O を用いて反応を試みたところ、目的物がわずか 9% しか得られなかった (entry 5)。そこで、銅塩に CuTc、溶媒に THF を用いる条件を最適条件とした。

**Table 3.1** Optimization of conjugate addition conditions.

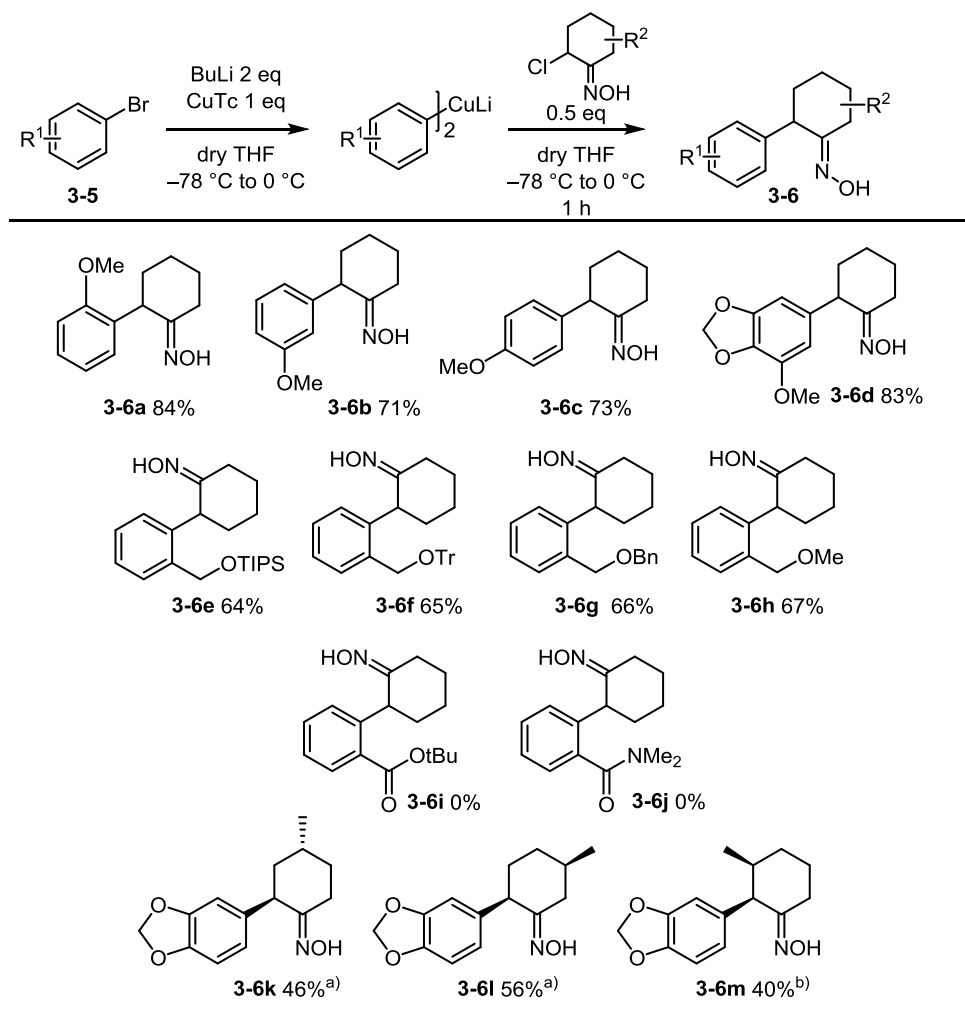


entry	Cu salt	solvent	yield
1	CuI	dry THF	75%
2	CuCN	dry THF	80%
3	CuOAc	dry THF	59%
4	CuTc	dry THF	85%
5	CuTc	dry Et <sub>2</sub> O	9%

### 第3節 基質の適用範囲の検討

次に、基質の適用範囲を調べた(**Table 3.2**)。まず臭化アリのールの基質適用範囲を調べた。ベンゼン環のオルト位、メタ位またはパラ位にメトキシ基のある基質を用いてそれぞれ反応を行ったところ、**3-6a~c** (*E* 体のみ) を良好な収率で得られた。ベンゼン環上に三つの置換基をもつ基質でも良好な収率で **3-6d** (*E* 体のみ) を与えた。また、ベンゼン環上に炭素側鎖を持つ4種の基質を用いて検討したところ、**3-6e~h** (*E* 体のみ) が良好な収率で得られた。しかしながら、アルコキシカルボニル基やアミノカルボニル基を持つ基質では、目的物 **3-6i** と **3-6j** が全く得られなかった。原因として、これらの置換基は有機銅試薬の生成を阻害されると推測した。次に、オキシム基質のシクロヘキサン環上の置換基効果を調べた。**3-5k** (*E/Z* = 3:1) と **3-5l** (*E/Z* = 3:1) を基質として検討したところ、目的物 **3-6k** (*E* 体のみ) と **3-6l** (*E* 体のみ) はそれぞれ46%、56%収率で得られた。目的物塩素原子の隣接位にメチル基がついた基質 **3-5m** (*E/Z* = 1:1) を用いた場合、**3-6m** (*E* 体のみ) は40%収率で得られたとともに *Z* 体の原料が31%回収された。やはり *Z*-体のオキシムの反応性が低いことが明らかになった。

**Table 3.2 Substrate scope of conjugate addition**



a) SM: *E/Z* 3:1.

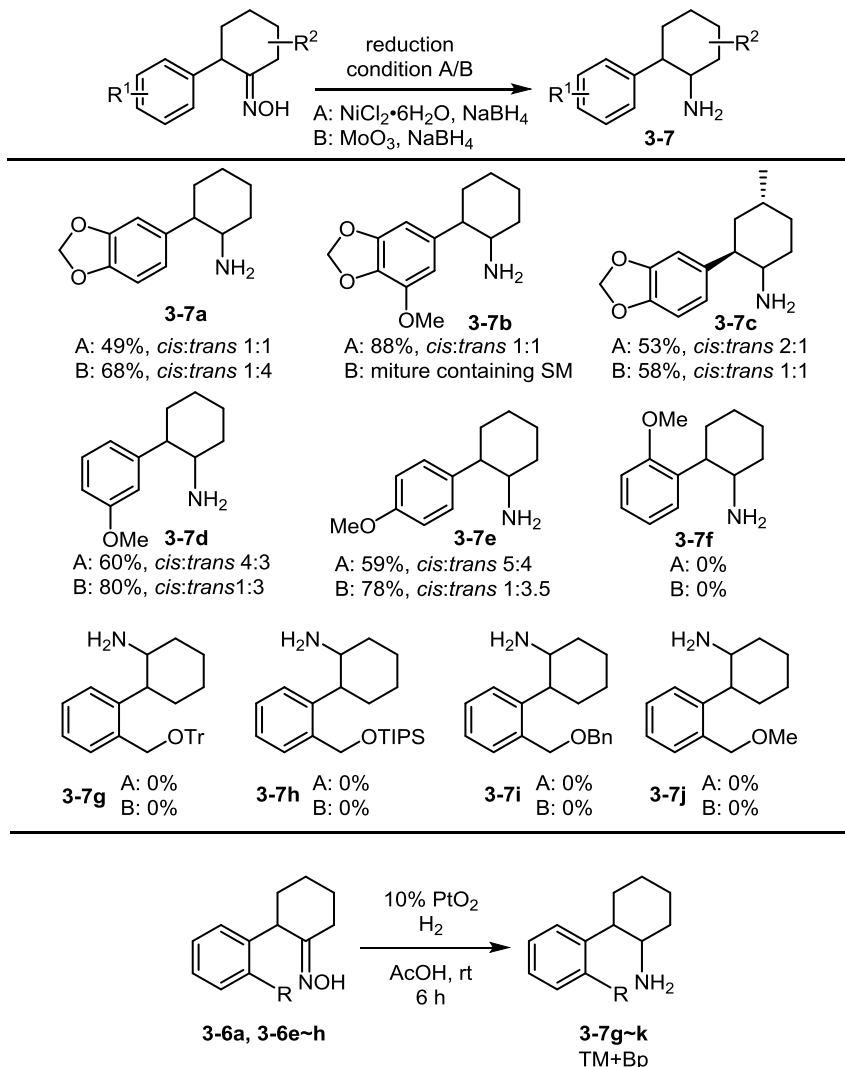
b) SM: *E/Z* 1:1, 31% of *Z*-SM was recovered.

#### 第4節 オキシム還元反応の検討

次に、オキシムの還元反応を検討した。まず水素化ホウ素ニッケルを用いる還元条件と酸化モリブデンと NaBH<sub>4</sub>を用いる還元条件を比較しながらそれぞれ検討した (Table 3.3)。結果として、水素化ホウ素ニッケルを用いる還元条件では *cis*-アミンが優先的に生成する傾向にあるのに反して、酸化モリブデンと NaBH<sub>4</sub>を用いる還元条件を用いた場合に *trans*-アミンが優先的に得られる傾向が見られた。また、オルト位に置換基のある基質はこの二つの条件下で還元反応が全く進行しないことが明らかになった。そこで、種々還元条件を検討した結果、AcOH 溶媒中でアダムズ触媒を用いる水添反応を試みたところ、オルト位に置換基のあ

る基質 **3-6e~h** の還元が進行し、目的のアミンと過剰還元された副生成物との混合物が得られた。

**Table 3.3 Reduction of  $\alpha$ -Aryl Oxime**

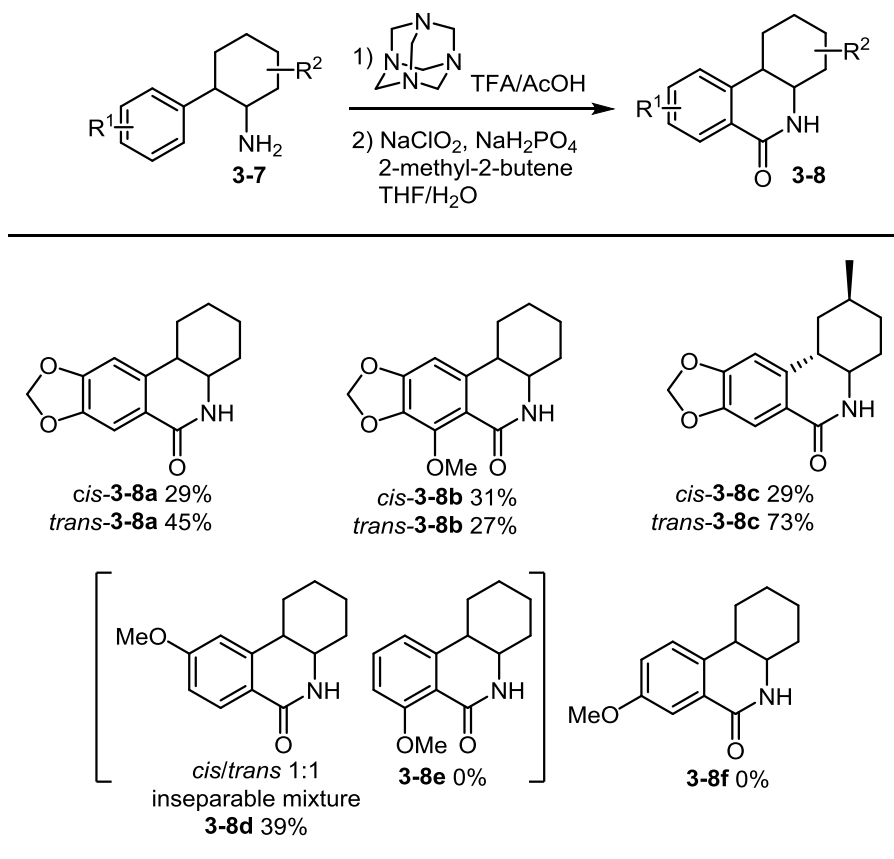


### 第5節 ラクタム環の形成による hexahydrophenanthridinone の合成

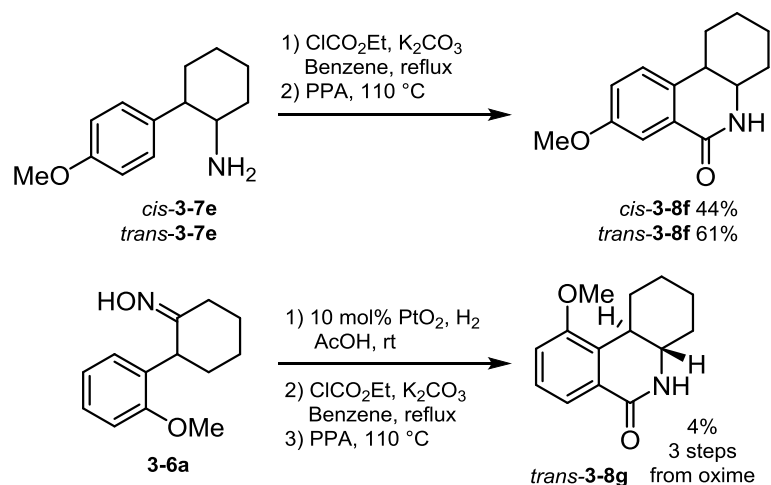
続いて、第4節で得られたアミンを用いてそれぞれラクタム環の形成を行った (**Table 3.4**)。アザアダマンタンを用いるホルミル化を行った後、得られたイミンを亜塩素酸ナトリウムで酸化してラクタムを得た。**3-7a~c** を用いた場合、*cis*-アミンと *trans*-アミン両方とも良好な収率でラクタム環を形成し対応する hexahydrophenanthridinone 化合物を与えている。アミン **3-7d** を用いた場合、位置選択的に反応が進行し、**3-8e** を生成することなく **3-8d** のみが得られ

た。**3-7e** を用いた場合にホルミル化が全く進行しなかった。メトキシ基のメタ位に電子密度が低いと推測した。

**Table 3.4 Lactam formation**



次に、**3-7e** を用いて Bischler–Napieralski 反応によるラクタム環形成<sup>2)</sup>を検討した (**Scheme 3.2**)。 *cis*-**3-7e** と *trans*-**3-7e** をそれぞれベンゾイン中でクロロギ酸メチルと反応させてカルバメートを合成してからポリリン酸 (PPA) を加えて加熱して反応を行ったところ、ラクタム環が形成した *cis*-**3-8f** と *trans*-**3-8f** がそれぞれ 44%、61% 収率で得られた。また、還元が困難であったオキシム **3-6a** をアダムズ触媒を用いる水添反応で還元した後、カルバメートに変換して同様に Bischler–Napieralski 反応条件に付したところ、低収率ながらラクタム環が形成した化合物 *trans*-**3-8g** が得られた。



**Scheme 3.2** Lactam formation via Bischler–Napieralski reaction.

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## 結論

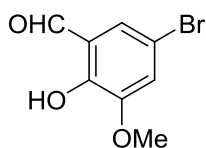
著者は *pancratistatin* 立体異性体の網羅的合成研究に取り組んだ。その結果、D-mannitol から NHC 触媒を用いる分子内不斉ベンゾイン環化反応と有機銅試薬の 1,4-付加反応とを含む 14 工程で *1,4a-di-epi-ent-pancratistatin* の全合成に成功した。合成した *1,4a-di-epi-ent-pancratistatin* およびその中間体を用いて活性評価を行ったところ、強力なフェロトキシ抑制活性を持つ新規化合物を見出した。また、*pancratistatin* 型天然物に共通する *hexahydrophenanthridinone* 三環性骨格の新規構築法を確立し、適用範囲の検討を行った。本骨格構築法を利用すれば、*pancratistatin* 型天然物及びその誘導体の構造活性相関研究や生物活性の発現機構の解明に必要な化合物を立体網羅的に供給できると期待できる。

## 実験項

### General Remarks

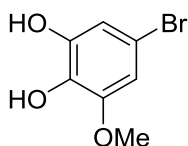
All anhydrous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents were purchased for the reactions and used without further desiccation. Analytical thin-layer chromatography was performed on Merck TLC silica gel 60F<sub>254</sub> silica gel plates. Visualization was accomplished with molybdenum phosphate, *p*-anisaldehyde, Hannessian's cocktail or ninhydrin. For column chromatography, silica gel (FUJI SILYSIA CHEMICAL LTD. BW-200) was employed. NMR spectra were recorded using a Bruker AV400N at 400 MHz frequency or JEOL JNM-AL300C at 300 MHz in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the  $\delta$  scale from an internal standard (NMR descriptions: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, oct = octet, m = multiplet, br = broad). Coupling constants, *J*, are reported in Hertz. Mass spectra were recorded on a Waters/Micromass SQD2, MICROMASS<sup>®</sup> LCT PREMIERTM (ESI-TOF). Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g·dL<sup>-1</sup>). IR was measured using a JEOL FT-IR 6200. Melting point was determined on J-SCIENCE RFS-10. Unless otherwise noted, reagents were used without further purification. HPLC analysis were performed on a SHIMADZU analytical system equipped with two LC-10AT pumps.

### 5-Bromo-2-hydroxy-3-methoxybenzaldehyde (2-34)



A mixture of *o*-vanilline (5.00 g, 32.9 mmol) and NaOAc (4.20 g, 49.4 mmol) were dissolved in glacial acetic acid (75 mL). A solution of bromine (2.5 mL, 49 mmol) in glacial acetic acid (25 mL) was added dropwise to the mixture over a period of 4 min. The solution deepened in colour throughout the addition, and was left to stir at room temperature for 1 h. The reaction was quenched with saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL). The resulting solution was adjusted to pH 5 by the addition of saturated solution of Na<sub>2</sub>CO<sub>3</sub> and NaHCO<sub>3</sub>, and the mixture was extracted with CHCl<sub>3</sub> (4 x 100 mL). The combined organic phases were washed with brine (400 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (7.00 g, 30.3 mmol, 92%) as yellow flakes of **mp** 119–122 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 11.01 (s, 1H), 9.86 (s, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.18, (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H). The <sup>1</sup>H NMR of **2-34** was identical to that reported.<sup>1)</sup>

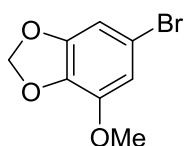
### 5-Bromo-3-methoxybenzene-1,2-diol (2-35)



Bromide **2-34** (7.00 g, 30.3 mmol) was dissolved in 2 M NaOH aq (30 mL, 0.06 mol). A mixture of 30% H<sub>2</sub>O<sub>2</sub> (7 mL, 0.06 mol) and H<sub>2</sub>O (28 mL) was added dropwise to the mixture. The mixture became deep red purple throughout the addition, and some white precipitate was observed. The mixture was stirred at room temperature until full consumption of starting material (1 h). The mixture was acidified with 2 M HCl (15 mL) and extracted with CHCl<sub>3</sub> (5 x 100 mL). The combined organic phases were washed with saturated solution of Na<sub>2</sub>SO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to afford **2-35** (4.91 g, 22.4 mmol, 74%) as light grey crystal of **mp** 75–76 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 6.77 (d, *J* = 2.0 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 5.33 (s, 1H), 5.31 (s, 1H), 3.87 (s, 3H). The <sup>1</sup>H NMR of **2-35** was identical to that reported.<sup>1)</sup>

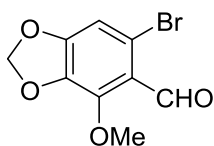
### 6-Bromo-4-methoxybenzo[d][1,3]dioxole (2-9)



To a solution of **2-35** (4.91 g, 22.4 mmol) in dry DMF (49 mL) were added K<sub>2</sub>CO<sub>3</sub> (7.00 g, 48.8 mmol)

and CH<sub>2</sub>Br<sub>2</sub> (2.5 mL, 3.7 mmol) under Ar at room temperature. After being stirred at 100 °C for 1.5 h, the solution was cooled to room temperature, diluted with H<sub>2</sub>O (900 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, evaporated in vacuo, and purified by silica gel column chromatography (hexane/CHCl<sub>3</sub> 5:1) to afford **2-9** (4.10 g, 17.7 mmol, 79%) as white solid of mp 78–79 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.68 (d, *J* = 1.5 Hz, 1H), 6.67 (d, *J* = 1.5 Hz, 1H), 5.97 (s, 2H), 3.88 (s, 3H). The <sup>1</sup>H NMR was identical to that reported.<sup>1)</sup>

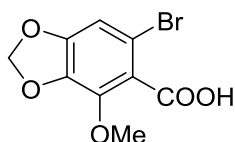
### 6-Bromo-4-methoxybenzo[d][1,3]dioxole-5-carbaldehyde (**2-36**)



To a stirred solution of **2-9** (4.10 g, 17.7 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) under argon cooled in a CO<sub>2</sub>–acetone bath, were added dichloromethyl methyl ether (2.1 mL, 18 mmol) and SnCl<sub>4</sub> (4.1 mL, 27 mmol). The mixture was warmed up to room temperature over 3 h. To the solution was added saturated aqueous solution of NaHCO<sub>3</sub>, and the whole was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were washed with 2 M HCl aq and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (hexane/acetone 9:1) to afford **2-36** (2.3 g, 8.9 mmol, 50%) as white solid of mp 117–120 °C.

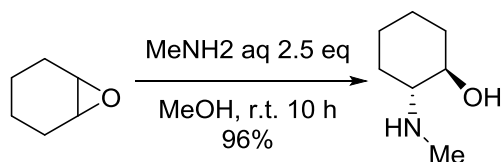
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.23 (s, 1 H), 6.86 (s, 1H), 6.05 (s, 2H), 4.03 (s, 3H). The <sup>1</sup>H NMR was identical to that reported.<sup>2)</sup>

### 6-bromo-4-methoxybenzo[d][1,3]dioxole-5-carboxylic acid (**2-38**)



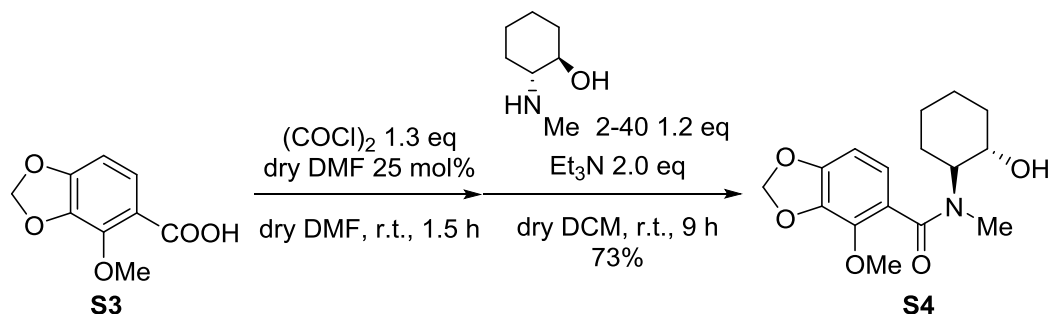
To a solution of compound **2-36** (0.60 g, 2.31 mmol) in <sup>t</sup>BuOH/H<sub>2</sub>O(5/1, 11 mL) were added NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O (5.50 g, 46.2 mmol), NaClO<sub>2</sub> (0.84 g 9.24 mmol), 2-methyl-2-butene (1.5 mL, 13.8 mmol) at room temperature. After being stirred at room temperature for 1 h, the solution was extracted with EtOAc (4 x 20 mL) and the combined organic layers were washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and recrystallized with Et<sub>2</sub>O to afford **2-38** (0.58 g, 2.13 mmol, 92%) as white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 6.78 (s, 1H), 6.01 (s, 2H), 4.05 (s, 3H) The <sup>1</sup>H NMR was identical to that reported.<sup>3)</sup>

### 2-(methylamino)cyclohexan-1-ol (**2-40**)



To a mixture of 40% MeNH<sub>2</sub>aq (6.87 mL, 78 mmol) and MeOH (8.6 mL) was added 1,2-epoxycyclohexane (2.96 mL, 29.9 mmol). After being stirred at room temperature for 10 h, the solution was evaporated in vacuo with toluene, and the residue purified by distillation under reduced pressure to afford **2-40** (2.17 g, 16.8 mmol, 56%) as colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.15~3.21 (m, 1H), 2.42 (s, 3H), 2.07~2.16 (m, 2H), 2.02~2.04 (m, 1H), 1.71~1.74 (m, 2H), 1.25~1.30 (m, 3H), 0.88~0.96 (m, 1H). The <sup>1</sup>H NMR was identical to that reported.<sup>4)</sup>

#### N-(2-hydroxycyclohexyl), N-methyl-4-methoxy-benzodioxole-5-carboxamide (**S4**)



To a solution of compound **S3**<sup>5)</sup> (200 mg, 1.02 mmol) in dry DCM 3.00 mL was added dry DMF (0.02 mL, 0.25 mmol), (COCl)<sub>2</sub> (0.11 mL 1.32 mmol). After being stirred at room temperature for 2 h, the solution was added dry DCM (3.0 mL), dry Et<sub>3</sub>N (0.27 mL 2.04 mmol) and a solution of **2-40** (184 mg, 1.22 mmol) in dry DCM 1.00 mL, at 0 °C. After being stirred at room temperature for 18 h, the solution was added 2M NaOH aq to adjust pH to 10 then the mixture was extracted with DCM for three times, washed with 1M HCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (Hexane/EtOAc 1/6) to afford **S4** (230 mg, 0.75 mmol 73%) as white solid.

**mp** 135~136 °C

**IR** (KBr): 3323, 2935, 2900, 2862, 1615, 1504, 1471, 1415, 1260, 1232, 1080, 1059, 1033 cm<sup>-1</sup>.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.80~6.78 (d, *J* = 8, 0.7 H), 6.65~6.63 (d, *J* = 8, 0.3H), 6.59~6.57 (d, *J* = 8, 1H) 6.01 (s, 2H), 4.02 (s, 3H), 3.5~3.7 (m, 1H), 3.14 (s, 0.5H), 3.02 (s, 1H), 2.77 (s, 2H), 2.2~2.1 (0.5H), 2.1~2.0 (m, 0.5H), 1.8~1.2 (m, 8H).

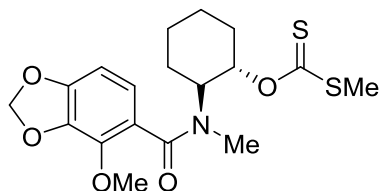
**<sup>13</sup>C NMR** (125.76 MHz, CDCl<sub>3</sub>): 169.3 (C), 150.0 (C), 138.4 (C), 136.4 (C), 123.8 (CH), 119.6 (C), 103.7 (CH), 101.4 (CH<sub>2</sub>), 69.6 (CH), 64.6 (CH), 60.5 (CH<sub>3</sub>), 34.5 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>).

**IR** (KBr): 3322, 2935, 1627, 1612, 1470, 1414, 1260, 1059.

**LRMS** (ESI) *m/z* 330 [M+Na]<sup>+</sup>.

**Anal. Calcd** for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: C, 62.53; H, 6.89; N, 4.53. Found: C, 61.96; H, 6.88; N, 4.50.

***O*-(2-(4-methoxy-*N*-methylbenzo[d][1,3]dioxole-5-carboxamido) cyclohexyl) *S*-methyl carbonodithioate (**S1a**)**



To a solution of sodium hydride (192 mg, 4.8 mmol) in THF (5 mL), compound **S4** (631 mg, 1.6 mmol) was added. The reaction mixture was stirred at room temperature for 10 mins. Cooled the reaction mixture to 0 °C and added carbon disulfide (0.11 mL, 1.6 mmol), stirred for 10 mins, followed by the addition of methyl iodide (0.11 mL, 1.6 mmol) at 0 °C. Allow to stir at room temperature for 3 h.

Reaction was monitored by TLC. After the completion of reaction, ice cold water (15 mL) was added extracted with ethyl acetate (25 mLx2). The combined organic layers were washed with water and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (Hexane/EtOAc 31) to afford (**S1a**) (618 mg, 1.56 mmol 97%) as pale yellow solid.

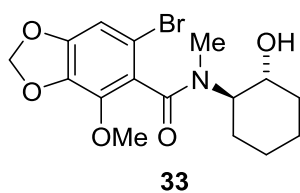
**mp** 69~70 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.92~6.90 (d, *J* = 8, 0.3H), 6.62~6.60 (d, 0.9H), 6.54~6.52 (d, *J* = 8, 0.8H) 6.00 (s, 0.4H) 5.96 (s, 1.6H), 5.79~5.66 (m, 1H), 4.88~5.10 (m, 0.6H), 4.00 (s, 3H), 3.74~3.64 (m, 0.4H), 2.95 (s, 1.1H), 2.72 (s, 1.9H), 2.60~2.50 (d, *J* = 12, 3H), 2.42~2.26 (m, 0.7H), 2.25~2.16 (m, 0.3H), 2.00~1.14 (m, 8H).

**<sup>13</sup>C NMR** (125.76 MHz, CDCl<sub>3</sub>): 215.9 (C), 169.4 (C), 149.8 (C), 139.8 (C), 135.9 (C), 123.4 (C), 122.1 (CH), 121.3 (CH), 120.2 (CH), 119.5 (CH), 103.1 (CH), 101.2 (CH), 98.5 (CH<sub>2</sub>), 80.4 (CH<sub>3</sub>), 70.1 (CH), 60.9 (CH<sub>3</sub>), 32.2 (CH<sub>3</sub>), 30.5 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 23.9 (CH<sub>2</sub>), 19.33 (CH<sub>3</sub>).

**LRMS** (ESI) *m/z*: 420 [M+Na]<sup>+</sup>.

**6-bromo-*N*-((1*R*,2*R*)-2-hydroxycyclohexyl)-4-methoxy-*N*-methylbenzo[d][1,3]dioxole-5-carboxamide (**2-41**)**



**33**

To a solution of compound **2-38** (0.50 g, 1.83 mmol) in dry DCM 10.0 mL was added dry DMF (0.04 mL, 0.46 mmol), (COCl)<sub>2</sub> (0.2 mL 2.38 mmol). After being stirred at room temperature for 2 h, the solution was added dry DCM (10.0 mL), dry Et<sub>3</sub>N (0.49 mL 3.66 mmol), compound **2-40** (0.33 g, 2.20 mmol) diluted with dry DCM (1.0 mL) at 0 °C. After being stirred at room temperature for 4 h, the solution was added 2M NaOH aq to adjust pH to 10 then the mixture was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with 1M HCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (Hexane/EtOAc = 1/1) to afford **2-41** (0.51, 1.31 mmol 72%) as white solid.

**mp** 132 ~ 134 °C

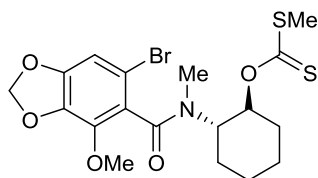
**IR** (KBr): 3441 (OH), 2929, 2854, 1741 (C=O), 1608, 1471, 1396, 1346, 1256, 1215, 1087, 1039, 525 (Br) cm<sup>-1</sup>.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.78~6.74 (m, 1 H), 6.01~5.96 (m, 2 H), 4.57~4.50 (m, 0.25 H), 4.38~4.30 (m, 0.25H), 4.02~3.98 (m, 3 H), 3.78~3.68 (m, 0.3 H), 3.65~3.50 (m, 0.7 H), 3.15~3.05(m, 1 H), 3.04 (s, 2 H), 2.46 (s, 0.25 H), 2.29 (s, 0.25 H), 2.20~2.00 (m, 1.5 H), 1.97~1.27 (m, 4 H), 1.35~1.25 (m, 2 H).

**<sup>13</sup>C NMR** (125.76 MHz, CDCl<sub>3</sub>): 167.8 (C), 167.0 (C), 150.0 (C), 139.6 (C), 136.1 (C), 125.3 (CH), 110.6 (C), 107.8 (CH), 101.9 (CH<sub>2</sub>), 70.0 (CH), 65.2 (CH), 60.6 (CH<sub>3</sub>), 34.1 (CH<sub>3</sub>), 29.4 (CH<sub>2</sub>), 27.9 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>).

**Anal. Calcd** for C<sub>16</sub>H<sub>20</sub>BrNO<sub>5</sub>: C, 49.76; H, 5.22; N, 3.63. Found: C, 49.46; H, 5.19; N, 3.83.

**O-((1R,2S)-2-(6-bromo-4-methoxy-N-methylbenzo[d][1,3]dioxole-5-carboxamido)cyclohexyl)-S-methyl carbonodithioate (S1b)**



**37**

To a solution of sodium hydride (133 mg, 3.33 mmol) in THF (5 mL), compound **2-41** (400 mg, 1.04 mmol) was added. The reaction mixture was stirred at room temperature for 10 mins. Cooled the reaction mixture to 0 °C and added carbon disulfide (0.07 mL, 1.11 mmol), stirred for 10 mins, followed by the addition of methyl iodide (0.08 mL, 1.11 mmol) at 0 °C. Allow to stir at room temperature for 2 h. Reaction was monitored by TLC. After the completion of reaction, ice cold water (15 mL) was added extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (Hexane/EtOAc = 2/1) to afford **S1b** (432 mg, 0.98 mmol 98%) as pale yellow solid.

**mp** 151~153 °C

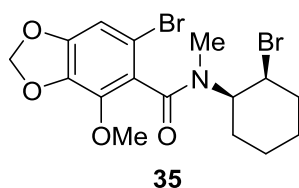
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.71 (s, 1 H), 5.95~5.93 (dd, 2 H), 5.79~5.72 (dt, 1 H) 5.07~5.01 (dt,

1 H), 4.01 (s, 3 H), 2.71 (s, 3 H), 2.55 (s, 3 H), 2.35~2.40 (m, 1 H), 1.85~2.04 (m, 1 H), 1.80~1.87 (m, 2 H), 1.64~1.44 (m, 3 H), 1.43~1.33 (m, 1 H);

<sup>13</sup>C NMR (125.76 MHz, CDCl<sub>3</sub>): 215.0 (C), 167.0 (C), 150.0 (C), 140.2 (C), 136.1 (C), 125.6 (C), 110.6 (CH), 107.3 (CH), 101.8 (CH), 80.2 (CH<sub>3</sub>), 65.8 (CH), 60.3 (CH<sub>3</sub>), 30.6 (CH<sub>3</sub>), 28.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 18.7 (CH<sub>2</sub>), 15.3 (CH<sub>3</sub>).

LRMS (ESI) m/z: [M+Na]<sup>+</sup> 498, 500.

### 6-bromo-N-((1R,2S)-2-bromocyclohexyl)-4-methoxy-N-methylbenzo[d][1,3]dioxole-5-carboxamide (S2)



To a solution of compound **2-41** (160 mg, 0.4 mmol) in dry DCM (2 mL), MsCl (0.06, 0.6 mmol) and Et<sub>3</sub>N (0.16 mL, 1.2 mmol) were added at 0 °C. After being stirred at room temperature for 3 hours, the reaction mixture was evaporated in vacuo. The residue was added H<sub>2</sub>O (10 mL), extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated solution of NaHCO<sub>3</sub>, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and then the residue was added anhydrous LiBr (73 mg, 0.8 mmol) and dry THF (1.5 mL) at 0 °C. After being stirred at room temperature for 5 hours, the reaction mixture was added H<sub>2</sub>O (10 mL), extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were directly dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and recrystallized with Et<sub>2</sub>O to afford **S2** (100 mg, 0.22 mmol, 56%) as pale yellow solid.

mp 172~173 °C (EtOAc/Hexane).

IR (KBr): 2929, 2860, 1746 (C=O), 1632, 1470, 1398, 1345, 1261, 1219, 1097, 1039, 526 (Br) cm<sup>-1</sup>.

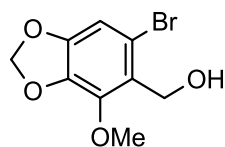
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.75~6.74 (d, *J* = 4, 1 H), 5.98~5.95 (m, 2 H), 3.98~3.97 (m, 3 H), 2.79~2.77 (m, 3 H), 2.55~2.45 (m, 1 H), 2.06~1.91 (m, 2H), 1.91~1.68 (m, 2 H), 1.60~1.40 (m, 3.5 H), 1.38~1.22 (m, 1.5 H).

<sup>13</sup>C NMR (125.76 MHz, CDCl<sub>3</sub>): 166.6 (C), 150.0 (C), 140.4 (C), 136.4 (C), 125.5 (C), 114.9 (CH), 110.5 (CH), 107.1 (CH), 101.8 (CH<sub>2</sub>), 60.2 (CH<sub>3</sub>), 51.4 (CH<sub>3</sub>), 37.8 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 24.8 (CH<sub>2</sub>), 18.0 (CH<sub>3</sub>).

Anal. Calcd for C<sub>16</sub>H<sub>19</sub>Br<sub>2</sub>NO<sub>4</sub>: C, 42.79; H, 4.26; N, 3.12. Found: C, 42.78; H, 4.31; N, 3.19.

### (6-Bromo-4-methoxybenzo[d][1,3]dioxol-5-yl)methanol (2-37)

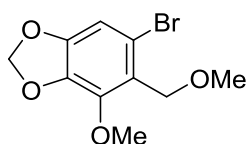




To a solution of **2-36** (8.30 g, 32.0 mmol) in THF (140 mL) cooled in an ice–water bath, were added NaBH<sub>4</sub> (1.84 g, 48.7 mmol) and EtOH (47 mL). The cooling bath was removed, and the mixture was stirred for 30 min. After the addition of saturated aqueous NH<sub>4</sub>Cl (25 mL), the whole was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo to give **2-37** as pale yellow solids (8.31 g), which was used directly in the next step without further purification. An analytical sample was obtained by recrystallization from hexane–EtOAc (2:1) as white blocks of mp 75–76 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 6.77 (s, 1H), 5.95 (s, 2H), 4.76 (d, *J* = 6.5 Hz, 2H), 4.05 (s, 3H), 2.12 (t, *J* = 6.5 Hz, 1H). The <sup>1</sup>H NMR was identical to that reported.<sup>6)</sup>

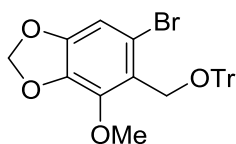
#### 6-Bromo-4-methoxy-5-(methoxymethyl)benzo[d][1,3]dioxole (**2-10**)



To a stirred solution of **2-37** (313 mg, 1.20 mmol) in THF (5 mL) was added 60% NaH in mineral oil (144 mg, 3.6 mmol) at room temperature. After 1 h, to the solution was added MeI (0.2 mL, 4 mmol) and then the mixture was heated under reflux. After 3.5 h, H<sub>2</sub>O (5 mL) was added and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc 9:1) to afford **2-10** (268 mg, 0.979 mmol, 70%) as yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.19 (s, 1H), 5.84 (s, 2H), 4.68 (s, 2H), 3.96 (s, 3H), 3.42 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 149.7 (C), 143.2 (C), 136.5 (C), 122.9 (C), 117.4 (C), 107.5 (CH), 101.6 (CH<sub>2</sub>), 68.2 (CH<sub>2</sub>), 60.3 (CH<sub>3</sub>), 58.1 (CH<sub>3</sub>).

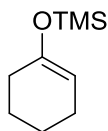
#### 6-Bromo-4-methoxy-5-(trityloxymethyl)benzo[d][1,3]dioxole (**2-14**)



To a stirred solution of **2-37** (261 mg, 1.00 mmol) in pyridine (8.0 mL) was added TrCl (558 mg, 2.00 mmol) at 100 °C. After 7 h, water (10 mL) was added and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and recrystallization from EtOH–CHCl<sub>3</sub> (4:1) gave **2-14** (322 mg, 0.642 mmol, 64%) as off-white needles of mp 173–174 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.56 (m, 6H), 7.30 (m, 6H), 7.24 (m, 3H), 6.77 (s, 1H), 5.95 (s, 2H), 4.19 (s, 2H), 3.90 (s, 3H). The <sup>1</sup>H NMR was identical to that reported.<sup>6)</sup>

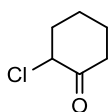
### 1-(Trimethylsiloxy)cyclohexene (2-43)



To a stirred solution of TMSCl (15 mL, 0.12 mol) and distilled Et<sub>3</sub>N (33 mL, 0.24 mol) in dry DMF (40 mL) was added cyclohexanone (10 mL, 0.10 mol). The mixture was heated under reflux at 155 °C for 22 h. During the reaction some pale yellow solids were formed (presumably triethylamine hydrochloride). After cooling to 25 °C, the mixture was diluted with pentane (200 mL); washed with a cold saturated aqueous solution of NaHCO<sub>3</sub> (3 x 100 mL), cold 2 M HCl aq (50 mL), and a cold saturated aqueous solution of NaHCO<sub>3</sub> (100 mL); dried over Na<sub>2</sub>SO<sub>4</sub>; and concentrated under pressure. Distillation of the remainder (70 °C/25 mmHg) afforded **2-43** (13.66 g, 80.22 mmol, 80%) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.86 (t, *J* = 4.0 Hz, 1H), 1.95–2.05 (m, 4H), 1.65 (m, 2H), 1.50 (m, 2H), 0.18 (s, 9H). The <sup>1</sup>H NMR was identical to that reported.<sup>7)</sup>

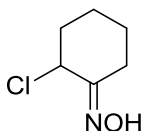
### 2-Chlorocyclohexan-1-one (2-44)



A 300 mL flask was charged with **2-43** (1.70 g, 10.0 mmol) in THF (100 mL). The solution was cooled to 0 °C and NCS (1.40 g, 10.5 mmol) was added in small portions over 6 min. Then, the mixture was poured into a 1:1 mixture of saturated aqueous solution of NaHCO<sub>3</sub> and brine (50 mL) and the whole was extracted with hexane (3 x 50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification of the resulting crude product by distillation (100 °C/8 mmHg) afforded **2-44** (0.86 g, 6.5 mmol, 65%) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.38 (m, 1H), 2.80 (m, 1H), 2.45–2.30 (m, 2H), 1.97–2.14 (m, 2H), 1.97–1.80 (m, 2H), 1.73 (m, 1H). The <sup>1</sup>H NMR was identical to that reported.<sup>7)</sup>

### 2-Chlorocyclohexan-1-one Oxime (2-7)

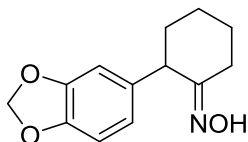


To a solution of hydroxylamine hydrochloride (417 mg, 6.01 mmol) and sodium acetate (492 mg, 6.00 mmol) in water (2 mL), was added **2-44** (531 mg, 4.00 mmol), and the mixture was stirred vigorously for 40 min. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting residue

was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **2-7** (253 mg, 1.72 mmol, 43%) a white solid of mp 81–82 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.17 (s, 1H), 4.69 (t, *J* = 3.0 Hz, 1H), 3.11 (m, 1H), 2.34–2.08 (m, 2H), 2.08–1.82 (m, 3H), 1.65 (m, 1H), 1.40 (m, 1H). The <sup>1</sup>H NMR was identical to that reported.<sup>7)</sup>

### 2-(Benzo[d][1,3]dioxol-5-yl)cyclohexan-1-one Oxime (3-4)



A 20 mL flask was charged with 5-bromobenzo[1,3]dioxole (0.100 mL, 0.800 mmol) in THF (3.0 mL). The solution was cooled to –78 °C, a 1.47 M hexane solution of BuLi (0.6 mL, 0.8 mmol) was added dropwise over 2 min, and then the mixture was stirred for 30 min to give a solution of the organolithium reagent. Another 20 mL flask was charged with CuCN powder (36 mg, 0.40 mmol) and THF (1.0 mL). To the mixture cooled at 0 °C, was slowly added the solution of the organolithium reagent. The mixture was stirred at this temperature for 20 min and then cooled to –78 °C. A solution of **2-7** (30 mg, 0.20 mmol) in THF (0.5 mL) was added slowly to this mixture. The mixture was stirred for 1 h at –78 °C and 1 h at 0 °C, and then brought to room temperature. The reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (5 mL) and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **3-4** (40 mg, 0.17 mmol, 86%) a pale yellow solid.

mp 151–152 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.75 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 3.40 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.97 (dt, *J* = 14.0, 4.0 Hz, 1H), 2.15 (m, 1H), 2.04–1.90 (m, 2H), 1.90–1.70 (m, 2H), 1.70–1.50 (m, 2H).

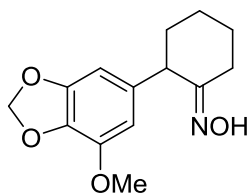
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 162.3 (C), 147.6 (C), 146.1 (C), 134.4 (C), 121.1 (CH), 108.8 (CH), 108.1 (CH), 100.9 (CH<sub>2</sub>), 47.8 (CH), 33.4 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 23.9 (CH<sub>2</sub>).

LRMS (ESI) (*m/z*): 232 [M – H]<sup>–</sup>.

HRMS (ESI) (*m/z*): [M – H]<sup>–</sup> calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>4</sub>, 232.0974; found, 232.0967.

IR (KBr): 3250, 2940, 2866, 1667, 1504, 1488, 1471, 1440, 1237, 1213, 1040, 725.

### 2-(7-Methoxybenzo[d][1,3]dioxol-5-yl)cyclohexan-1-one Oxime (3-6d)



A 20 mL flask was charged with **2-9** (185 mg, 0.800 mmol) and THF (3.0 mL). The resulting solution

was cooled to  $-78\text{ }^{\circ}\text{C}$  and a 1.47 M hexane solution of BuLi (0.600 mL, 0.800 mmol) was added dropwise over 2 min and then the mixture was stirred for 30 min to give a solution of the organolithium reagent. Another 20 mL flask was charged with CuCN powder (36 mg, 0.40 mmol) and THF (1.0 mL). To the mixture cooled at  $0\text{ }^{\circ}\text{C}$ , was slowly added the solution of the organolithium reagent. The mixture was stirred at this temperature for 20 min and then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of **2-7** (30 mg, 0.20 mmol) in THF (0.5 mL) was added slowly to this mixture. The mixture was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$  and 1 h at  $0\text{ }^{\circ}\text{C}$ , and then brought to room temperature. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **3-6d** (40 mg, 0.15 mmol, 76%) a white solid.

**mp** 153–154  $^{\circ}\text{C}$ .

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.43 (s, 1H), 6.38 (s, 1H), 5.99 (s, 2H), 3.86 (s, 3H), 3.37 (dd,  $J = 9.0, 5.5$  Hz, 1H), 3.00 (dt,  $J = 14.0, 4.0$  Hz, 1H), 2.10 (m, 1H), 2.04–1.90 (m, 2H), 1.90–1.70 (m, 2H), 1.70–1.50 (m, 2H).

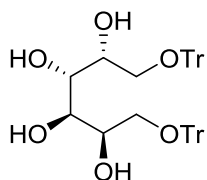
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.2 (C), 148.8 (C), 143.4 (C), 135.2 (C), 133.8 (C), 107.9 (CH), 102.4 (CH), 101.3 ( $\text{CH}_2$ ), 56.6 ( $\text{CH}_3$ ), 48.1 (CH), 33.5 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 24.0 ( $\text{CH}_2$ ).

**LRMS** (ESI) ( $m/z$ ): 262 [ $\text{M}-\text{H}$ ] $^-$ ;

**HRMS** (ESI) ( $m/z$ ): [ $\text{M}-\text{H}$ ] $^-$  calcd for  $\text{C}_{14}\text{H}_{15}\text{NO}_4$ , 262.1079; found, 262.1089.

**IR** (KBr): 3210, 2941, 2879, 2784, 1634, 1509, 1450, 1430, 1238, 1044.

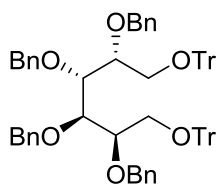
### 1,6-Bis-*O*-(triphenylmethyl)-*D*-mannitol (**2-45**)



To a solution of *D*-mannitol (5.46 g, 30.0 mmol) in pyridine (60 mL) was added trityl chloride (18.4 g, 66.0 mmol), and the mixture was heated under reflux for 1.5 h. The volatiles were removed under reduced pressure, and the residue was partitioned between DCM and saturated  $\text{NaHCO}_3$ . The aqueous phase was extracted with DCM until no product remained in the aqueous layer (TLC), and the combined organic extracts were washed with a further portion of saturated  $\text{NaHCO}_3$  before drying ( $\text{Na}_2\text{SO}_4$ ) and concentrating under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc 1:1) to give **2-45** (16.8 g, 25.2 mmol, 84%).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.14 (m, 30H), 3.87 (t,  $J = 6.5$  Hz, 2H), 3.74 (t,  $J = 6.5$  Hz, 2H), 3.43 (d,  $J = 5.0$  Hz, 2H), 3.29–3.20 (m, 6H). The  $^1\text{H}$  NMR was identical to that reported.<sup>8)</sup>

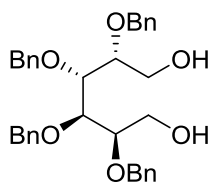
### 2,3,4,5-Tetra-*O*-benzyl-1,6-bis-*O*-(triphenylmethyl)-*D*-mannitol (**2-46**)



To a solution of **2-45** (1.06 g, 1.50 mmol) in THF (9.0 mL) under Ar was added benzyl bromide (0.600 mL, 7.00 mmol). A 60% oil dispersion of NaH (288 mg, 7.20 mmol) was added gradually, and the mixture was stirred for 6 h and then heated under reflux overnight before careful quenching with MeOH. The solvent was removed under reduced pressure, and the residue was partitioned between H<sub>2</sub>O and DCM. The organic phase was washed with a further portion of H<sub>2</sub>O before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. **2-46** (942 mg, 0.916 mmol, 61%) was purified by silica gel column chromatography (hexane/EtOAc 9:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.50–7.42 (m, 12 H), 7.38 (d, *J* = 8.0 Hz, 4H), 7.32 (q, *J* = 8.0, 24.0 Hz, 4H), 7.20–7.10 (m, 26H), 6.93 (d, *J* = 8.0 Hz, 4H), 4.74 (d, *J* = 12.0 Hz, 2H), 4.40 (q, *J* = 8.0, 32.0 Hz, 4 H), 4.35 (d, *J* = 12.0 Hz, 2H), 4.25 (d, *J* = 8.0 Hz, 2H), 3.90–3.80 (m, 2H), 3.65 (d, *J* = 8.0 Hz, 2H), 3.28 (dd, *J* = 4.0, 8.0 Hz, 2H). The <sup>1</sup>H NMR was identical to that reported.<sup>9)</sup>

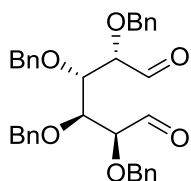
#### 2,3,4,5-Tetra-*O*-benzyl-D-mannitol (**2-47**)



To a solution of **2-46** (942 mg, 0.916 mmol) in a 2:1 mixture of MeOH/ CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added TFA (1.00 mL), and the mixture was stirred overnight. The mixture was neutralized using saturated aqueous NaHCO<sub>3</sub> solution, and after ensuring no acid remained, the organic phase was collected, and the aqueous phase was extracted twice with DCM. The combined organic extracts were washed with a further portion of saturated NaHCO<sub>3</sub> before being dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 2:3) affording **2-47** (375 mg, 0.692 mmol, 77%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.36–7.26 (m, 20H), 4.76 (d, *J* = 12.0 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.56 (d, *J* = 12.0 Hz, 2H), 4.41 (d, *J* = 12.0 Hz, 2H), 3.95–3.87 (m, 2H), 3.70–3.65 (q, *J* = 4.0, 12.0 Hz, 2H). The <sup>1</sup>H NMR was identical to that reported.<sup>9)</sup>

#### 2,3,4,5-Tetra-*O*-benzyl-D-manno-hexodialdose (**1-19**)

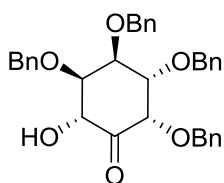


To a solution of distilled DMSO (0.19 mL, 2.7 mmol) in distilled CH<sub>2</sub>Cl<sub>2</sub> (6.00 mL) at –78 °C under Ar was added a solution of distilled (COCl)<sub>2</sub> (0.230 mL, 2.70 mmol) in distilled CH<sub>2</sub>Cl<sub>2</sub> (2.80 mL)

slowly via syringe. The solution was stirred for 10 min before a solution of **2-47** (567 mg, 1.04 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5.50 mL) was added slowly via syringe, and the mixture was stirred for a further 1 h. Distilled Et<sub>3</sub>N (1.40 mL, 10.0 mmol) was added, and the mixture was stirred at -78 °C for 15 min before being allowed to warm up to room temperature (ca. 1.5 h). The solvent was removed under reduced pressure, and the residue was suspended in a 1:1 mixture of hexane and EtOAc (20 mL) and then filtered. The filtrate was concentrated under reduced pressure affording the crude **1-19** (566 mg, 1.00 mmol) that were used without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.70 (s, 2H), 7.40–7.26 (m, 16H), 7.24–7.18 (m, 4H), 4.65 (d, *J* = 12.0 Hz, 2H), 4.60 (d, *J* = 12.0 Hz, 2H), 4.50 (d, *J* = 12.0 Hz, 2H), 4.42 (d, *J* = 12.0 Hz, 2H), 4.04 (s, 2H). The <sup>1</sup>H NMR was identical to that reported.<sup>10)</sup>

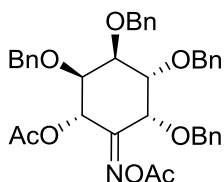
### D-allo-3-Inosose (**1-20**)



The crude **1-19** (566 mg, 1.00 mmol) was evaporated after the addition of toluene (2 mL) to remove EtOAc, and the residue was dissolved in toluene (3 mL). To a suspension of the triazolium salt (24 mg, 0.05 mmol) in toluene (5.5 mL), a 1% v/v solution of Et<sub>3</sub>N in toluene (0.70 mL, 0.050 mmol) was added, and after 30 min, the above solution of **1-19** was added. After 45 min, the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (toluene/EtOAc 40/1 to 20/1) to give **1-20** (262 mg, 0.487 mmol, 49%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.40–7.26 (m, 16H), 7.16–7.10 (m, 4H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.61–4.58 (m, 2H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 3.94 (t, *J* = 3.0 Hz, 1H), 3.78–3.75 (m, 2H), 3.52 (d, *J* = 3 Hz, 1H). The <sup>1</sup>H NMR was identical to that reported.<sup>10)</sup>

### (1*S*,3*R*,4*R*,5*S*,6*R*)-2-Acetoxyimino-3,4,5,6-tetrakisbenzyloxy-cyclohexyl acetate (**2-21**)



To a solution of **1-12** (884 mg, 1.64 mmol) in pyridine (15 mL), was added NH<sub>2</sub>OH·HCl (568 mg, 8.20 mmol), and the solution was stirred at rt for 1.5 h. The solution was diluted with EtOAc (20 mL), washed with H<sub>2</sub>O (20 mL x 3) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to give crude oxime as a pale brown oil; yield: 710 mg. The above oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (6.00 mL), and pyridine (1.00 mL, 12.8 mmol), DMAP (10 mg, 0.26 mmol), and Ac<sub>2</sub>O (1.30 mL, 12.8 mmol) were added to the stirred solution cooled in an ice-water bath. The mixture was stirred for 2 h, and the

reaction was quenched by the addition of H<sub>2</sub>O (10 mL). The whole was extracted with CHCl<sub>3</sub> (3 x 20 mL), and the combined organic layers were washed with brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give **2-21** (511 mg, 0.801 mmol, 49%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.40–7.25 (m, 40H), 6.04 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.58 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.08 (dd, *J* = 1.5, 3.5 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 2H), 4.74 (dd, *J* = 4.5, 12.0 Hz, 2H), 4.66 (dd, *J* = 5.0, 12.5 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 4.60 (d, *J* = 12.0 Hz, 2H), 4.57 (dd, *J* = 4.0, 12.0 Hz, 2H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.28 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.26 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.06 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.97 (m, 2H), 3.95 (dd, *J* = 3.5, 10.0 Hz, 1H), 2.15 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H).

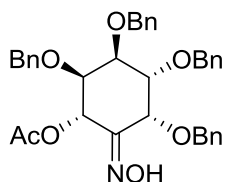
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 169.5 (C), 169.4 (C), 167.8 (C x 2), 157.9 (C), 157.4 (C), 138.6 (C), 138.5 (C), 138.4 (C), 138.2 (C), 137.7 (C), 137.5 (C x 2), 137.3 (C), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH x 2), 127.6 (CH), 78.0 (CH), 77.9 (CH), 75.9 (CH), 75.7 (CH), 75.6 (CH), 73.8 (CH<sub>2</sub>), 73.6 (CH<sub>2</sub>), 73.4 (CH<sub>2</sub>), 73.0 (CH<sub>2</sub>), 72.6 (CH<sub>2</sub>), 72.5 (CH<sub>2</sub>), 71.1 (CH), 71.0 (CH<sub>2</sub>), 69.2 (CH), 20.8 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>), 19.4 (CH<sub>3</sub>).

LRMS (ESI) *m/z* 660 (M + Na).

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>38</sub>H<sub>39</sub>NO<sub>8</sub>Na, 660.2573; found, 660.2562.

IR (neat): 3542, 3087, 3063, 3030, 2870, 1779, 1752, 1637.

**(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4,5-Tetrakisbenzyloxy-6-hydroxyiminocyclohexyl acetate (2-22)**



To an ice-cold solution of **2-21** (511 mg, 0.800 mmol) in MeOH (40 mL) was added dropwise, over 20 min, a 0.2 M solution of MeNH<sub>2</sub> in MeOH (4 mL, 0.8 mmol). The mixture was immediately concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give **2-22** (386 mg, 0.648 mmol, 81% yield) as a yellow oil.

[α]<sub>D</sub><sup>28</sup> 71.73 (*c* 1.00, CHCl<sub>3</sub>)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.40–7.27 (m, 40H), 6.27 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.44 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.28 (dd, *J* = 1.5, 4.0 Hz, 1H), 4.83 (t, *J* = 11.5 Hz, 2H), 4.76 (d, *J* = 4.0 Hz, 1H), 4.73 (d, *J* = 4.0 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 2H), 4.66 (d, *J* = 4.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 4.62 (d, *J* = 12.0 Hz, 2H), 4.58 (d, *J* = 12.0 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 2H), 4.36 (dd, *J* = 6.5, 12.5 Hz, 2H), 4.30 (dd, *J* = 1.5, 4.0 Hz, 1H), 4.27 (t, *J* = 3.0 Hz, 1H), 4.01 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.95 (t, *J* = 4.0 Hz, 1H), 3.90 (t, *J* = 3.5 Hz, 1H), 1.91 (s, 3H x 2).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.0 (C x 2), 151.0 (C x 2), 150.4 (C x 2), 138.7 (C x 2), 138.6 (C x 2), 138.1 (C), 137.8 (C), 137.6 (C x 2), 128.3 (C x 4), 128.2 (C x 2), 128.1 (C), 128.0 (C), 127.9 (C), 127.8 (C), 127.6 (C), 127.5 (C x 3), 127.4 (C), 77.9 (CH), 76.0 (CH), 75.5 (CH), 75.3 (CH), 75.0 (CH),

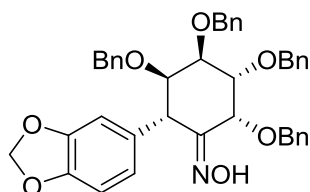
73.6 (CH<sub>2</sub>), 72.5 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 71.5 (CH), 71.0 (CH<sub>2</sub>), 69.8 (CH<sub>2</sub>), 67.4 (CH), 21.0 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>).

**LRMS** (ESI)  $m/z$  618 (M + Na).

**HRMS** (ESI) ( $m/z$ ): [M+Na]<sup>+</sup> calcd for C<sub>36</sub>H<sub>37</sub>NO<sub>7</sub>Na, 618.2468; found, 618.2480.

**IR** (neat): 3324, 3063, 3030, 2872, 1740, 1496, 1454, 1371, 1227, 1113.

**(2*S*,3*R*,4*R*,5*R*,6*R*)-2-(Benzo[d][1,3]dioxol-5-yl)-3,4,5,6-tetrakisbenzyloxy-cyclohexan-1-one oxime (2-23)**



A 20 mL flask was charged with 5-bromobenzo[1,3]dioxole (0.25 mL, 2.0 mmol) and THF (10.0 mL). The resulting solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and a 1.43 M hexane solution of BuLi (1.40 mL, 2.00 mmol) was added dropwise over 2 min and then the mixture was stirred for 30 min to give a solution of the organolithium reagent. Another 20 mL flask was charged with CuCN powder (100 mg, 1.00 mmol) and THF (4.0 mL). To the mixture cooled at  $0\text{ }^{\circ}\text{C}$ , the solution of the organolithium reagent was added via a cannula over 10 min. The mixture was stirred at this temperature for 20 min and then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of **2-22** (276 mg, 0.462 mmol) in THF (2.0 mL) was added to this mixture via a cannula over 3 min. The mixture was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$  and 1 h at  $0\text{ }^{\circ}\text{C}$ , and then brought to rt. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **2-23** (48 mg, 0.073 mmol, 16% yield) as a yellow oil.

$[\alpha]_{\text{D}}^{19} -23.52$  ( $c$  0.50, CHCl<sub>3</sub>)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.60 (s, 1H), 7.40–7.28 (m, 15H), 7.22–7.18 (m, 3H), 7.08–7.02 (m, 2H), 6.66 (s, 1H), 6.55 (d,  $J = 8.0$  Hz, 1H), 6.40 (d,  $J = 8.0$  Hz, 1H), 5.84 (s, 1H), 5.78 (s, 1H), 5.28 (d,  $J = 4.0$  Hz, 1H), 4.85 (d,  $J = 12.0$  Hz, 1H), 4.71 (d,  $J = 12.0$  Hz, 1H), 4.65 (d,  $J = 12.0$  Hz, 1H), 4.64 (s, 2H), 4.58 (d,  $J = 12.0$  Hz, 1H), 4.31 (dd,  $J = 2.5, 9.0$  Hz, 1H), 4.24 (t,  $J = 5.5$  Hz, 1H), 4.19 (s, 2H), 4.00 (dd,  $J = 4.0, 9.0$  Hz, 1H), 3.88 (d,  $J = 4$  Hz, 1H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>):  $\delta$  156.1 (C), 147.6 (C), 146.0 (C), 138.9 (C), 138.7 (C), 138.2 (C), 137.9 (C), 131.8 (C), 128.4 (CH x 2), 128.3 (CH x 2), 128.1 (CH x 2), 128.0 (CH), 127.9 (CH x 2), 127.8 (CH), 127.7 (CH x 2), 127.6 (CH x 2), 127.4 (CH), 127.2 (CH), 119.5 (CH), 107.9 (CH), 107.7 (CH), 100.8 (CH<sub>2</sub>), 78.0 (CH), 77.1 (CH), 75.8 (CH), 73.5 (CH<sub>2</sub>), 72.2 (CH<sub>2</sub> x 2), 71.1 (CH<sub>2</sub>), 68.4 (CH), 47.6 (CH).

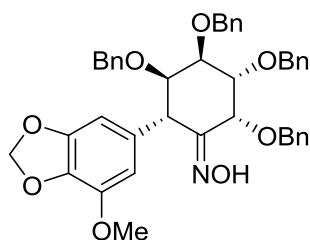
**LRMS** (ESI)  $m/z$  680 (M + Na).

**HRMS** (ESI) ( $m/z$ ): [M+Na]<sup>+</sup> calcd for C<sub>41</sub>H<sub>39</sub>NO<sub>7</sub>Na, 680.2624; found, 680.2595.

**IR** (neat): 3326, 3064, 3030, 2893, 1503, 1489, 1455, 1216, 1101, 1040.



**(2R,3R,4R,5R,6S)-2,3,4,5-Tetrakis(benzyloxy)-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclohexan-1-one oxime (2-24)**



A 20 mL flask was charged with 6-bromo-4-methoxybenzo[d][1,3]dioxole (**2-9**) (185 mg, 0.801 mmol) and THF (3.0 mL). The resulting solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and a 1.43 M hexane solution of BuLi (0.60 mL, 0.80 mmol) was added dropwise over 1 min and then the mixture was stirred for 30 min to give a solution of the organolithium reagent. Another 20 mL flask was charged with CuCN powder (36 mg, 0.40 mmol) and THF (1.0 mL). To the mixture cooled at  $0\text{ }^{\circ}\text{C}$ , was added the solution of the organolithium reagent via a cannula over 5 min. The mixture was stirred at this temperature for 20 min and then cooled to  $-78\text{ }^{\circ}\text{C}$ . A solution of **2-22** (125 mg, 0.210 mmol) in THF (0.5 mL) was added to this mixture via a cannula over 2 min. The mixture was stirred for 1 h at  $-78\text{ }^{\circ}\text{C}$  and 1 h at  $0\text{ }^{\circ}\text{C}$ , and then brought to rt. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL) and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **2-24** (30 mg, 0.044 mmol, 22% yield) as a yellow oil.

$[\alpha]_{\text{D}}^{21} -18.31$  ( $c$  1.00,  $\text{CHCl}_3$ )

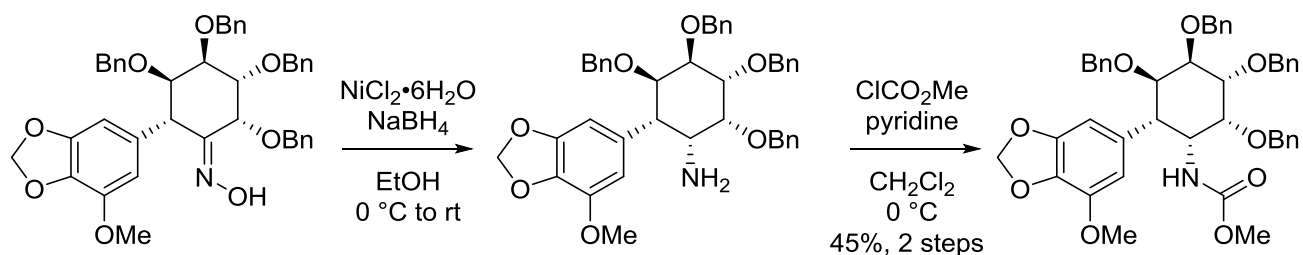
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.53 (s, 1H), 7.37–7.25 (m, 15H), 7.23–7.20 (m, 3H), 7.13–7.11 (m, 2H), 6.37 (s, 1H), 6.31 (s, 1H), 5.84 (dd,  $J = 1.5, 5.5$  Hz, 2H), 5.31 (d,  $J = 3.5$  Hz, 1H), 4.83 (d,  $J = 12.0$  Hz, 1H), 4.70 (d,  $J = 12.0$  Hz, 1H), 4.64 (d,  $J = 12.0$  Hz, 1H), 4.63 (s, 2H), 4.57 (d,  $J = 12.0$  Hz, 1H), 4.30 (dd,  $J = 2.5, 9.0$  Hz, 1H), 4.27 (s, 2H), 4.25 (t,  $J = 3.5$  Hz, 1H), 4.00 (dd,  $J = 3.5, 8.5$  Hz, 1H), 3.90 (d,  $J = 4$  Hz, 1H), 3.53 (s, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.0 (C), 148.8 (C), 143.2 (C), 138.8 (C), 138.6 (C), 138.2 (C), 137.8 (C), 133.8 (C), 132.8 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH x 2), 128.0 (CH), 127.9 (CH x 2), 127.8 (CH), 127.7 (CH x 2), 127.6 (CH x 3), 127.5 (CH), 127.4 (CH), 107.1 (CH), 101.5 (CH), 101.3 ( $\text{CH}_2$ ), 77.9 (CH), 77.4 (CH), 76.7 (CH), 73.3 ( $\text{CH}_2$ ), 72.4 ( $\text{CH}_2$  x 2), 71.6 ( $\text{CH}_2$ ), 68.6 (CH), 58.2 (CH), 56.5 ( $\text{CH}_3$ ).

**LRMS** (ESI)  $m/z$  710 (M + Na).

**HRMS** (ESI) ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{42}\text{H}_{41}\text{NO}_8\text{Na}$ , 710.2730; found, 710.2700. **IR** (neat): 3333, 3063, 3030, 2927, 1718, 1633, 1496, 1453, 1206, 1090, 1040.

**methyl((1R,2R,3R,4R,5R,6S)-2,3,4,5-tetrakis(benzyloxy)-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclohexyl) carbamate (2-26)**



A 20 mL flask was charged with **2-24** (135 mg, 0.196 mmol) EtOH (3.0 mL).and NiCl<sub>2</sub>·6H<sub>2</sub>O (132 mg, 0.392 mmol). To the mixture cooled in an ice–water bath, NaBH<sub>4</sub> (106 mg, 2.85 mmol) was portion-wise added, and the cooling bath was removed. After 1.5 h, the mixture was cooled in an ice–water bath, NaBH<sub>4</sub> (106 mg, 2.85 mmol) was portion-wise added again. The mixture was stirred at rt for 2 h and diluted with EtOAc (20 mL). After addition of H<sub>2</sub>O (20 mL), the whole was filtered through celite pad, which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give crude amine **2-25** as a pale purple oil (140 mg).

A solution of the above oil and pyridine (0.05 mL, 0.062 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) was added via cannular to a stirred solution of methyl chloroformate (0.05 mL, 0.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 90 min, saturated aqueous NaHCO<sub>3</sub> (20 mL) was added, and the organic phase was washed with saturated aqueous NH<sub>4</sub>Cl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 4:1) to give **2-26** (65 mg, 0.088 mmol, 45%) as a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.37–7.25 (m, 16H), 7.22–7.12 (m, 2H), 7.10–7.02 (m, 2H), 6.42 (d, *J* = 4.0 Hz, 1H), 5.92 (s, 2H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.45 (dd, *J* = 3.5, 6.6 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 3.96 (dd, *J* = 2.5, 12.0 Hz, 1H), 3.92 (d, d, *J* = 3.5 Hz, 1H), 3.82 (d, *J* = 2.5 Hz, 1H x 2), 3.51 (s, 3H), 3.31 (dd, *J* = 3.5, 12.0 Hz, 1H).

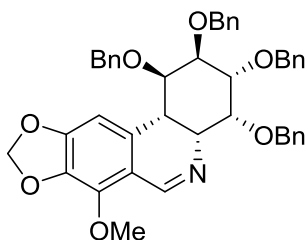
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 157.2 (C), 148.4 (C), 143.2 (C), 138.5 (C), 138.2 (C), 137.9 (C), 137.9 (C), 133.9 (C), 133.6 (C), 128.6 (CH), 128.5 (CH), 128.4 (CH x 2), 128.3 (CH), 128.3 (CH x 2), 128.2 (CH), 128.1 (CH x 2), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH x2), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 108.5 (CH), 103.0 (CH), 101.1 (CH<sub>2</sub>), 79.1 (CH), 74.7 (CH), 74.4 (CH), 74.1 (CH<sub>2</sub>), 73.9 (CH), 73.0 (CH<sub>2</sub>), 71.9 (CH<sub>2</sub>), 70.7 (CH<sub>2</sub>), 56.4 (CH<sub>3</sub>), 53.3 (CH), 51.9 (CH<sub>3</sub>), 46.0 (CH).

LRMS (ESI) *m/z* 754(M + Na).

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>44</sub>H<sub>45</sub>NO<sub>9</sub>Na, 754.2992; found, 754.2988.

IR (neat): 3413, 3087, 3063, 3029, 3004, 2876, 1729, 1635, 1513, 1453, 1360, 1320, 1232, 1045, 911, 734, 699.

**(1*R*,2*R*,3*R*,4*R*,4*aR*,11*bS*)-1,2,3,4-tetrakis(benzyloxy)-7-methoxy-1,2,3,4,4*a*,11*b*-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (2-28)**



To a solution of amine **2-25** (106 mg, 0.15 mmol) in AcOH:TFA (2.4 mL, 3:1) at room temperature was added hexamethylenetetramine (112 mg, 0.75 mmol) and the resulting mixture was heated to 90 °C and stirred for 5 h until complete conversion. The reaction mixture was concentrated under reduced pressure and dissolved in MeOH (10 mL) and NaHCO<sub>3</sub> (4.8 g) was carefully added. The mixture was then loaded onto Celite pad which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give crude imine which was purified by silica gel column chromatography (hexane/EtOAc 1:2) to give **2-28** (67 mg, 0.088 mmol, 65%) as a yellow oil.

$[\alpha]_D^{28}$  36.08 (*c* 1.01, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.64 (s, 1H), 7.37–7.10 (m, 18H), 7.00 (s, 2H), 6.51 (s, 1H), 5.93 (d, *J* = 8.0 Hz, 2H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.70 (t, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 2H), 4.54 (t, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.04 (s, 3H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.94 (d, *J* = 12.0 Hz, 2H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 1H), 3.62 (d, *J* = 10.5 Hz, 1H), 2.96 (dd, *J* = 4.5, 10.5 Hz, 1H).

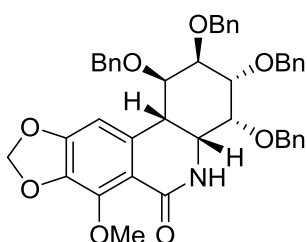
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 153.1 (CH), 150.5 (C), 141.2 (C), 139.5 (C), 138.7 (C), 138.6 (C), 138.2 (C), 134.9 (C), 133.5 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH x 2), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH x2), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 114.3 (C), 105.5 (CH), 101.1 (CH<sub>2</sub>), 76.3 (CH), 75.4 (CH), 75.3 (CH), 74.3 (CH), 73.1 (CH<sub>2</sub>), 73.0 (CH<sub>2</sub>), 72.2 (CH<sub>2</sub>), 71.0 (CH<sub>2</sub>), 60.0 (CH<sub>3</sub>), 57.4 (CH), 36.7 (CH).

**LRMS** (ESI) *m/z* 706 (M + Na).

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>43</sub>H<sub>41</sub>NNaO<sub>7</sub>, 684.2961; found, 684.2949.

**IR** (neat): 3086, 3062, 3029, 2869, 1730, 1689, 1631, 1597, 1496, 1479, 1454, 1376, 1304, 1235, 1096, 1045, 1028, 910, 874, 734, 698.

**(1R,2R,3R,4R,11bS)-1,2,3,4-tetrakis(benzyloxy)-7-methoxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (2-27)**



To a solution of imine **2-28** (79 mg, 0.11 mmol) in THF (1.1 mL) were added 2-methyl-2-butene (0.64 mL, 5.5 mmol), water (1.1 mL), NaH<sub>2</sub>PO<sub>4</sub>•2H<sub>2</sub>O (246 g, 2.20 mmol), and NaClO<sub>2</sub> (330 mg, 2.20 mmol) at 0 °C. The mixture was warmed to roomtemperature slowly in an ice–water bath. Then, saturated aqueous Na<sub>2</sub>SO<sub>3</sub> (5 mL) was added, and the whole was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound **2-27** (58 mg, 74%) as pale yellow oil. [ $\alpha$ ]<sub>D</sub><sup>28</sup> 117.67 (*c* 1.02, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.40–7.20 (m, 16H), 7.18 (dt, *J* = 8.0 Hz, 2 Hz, 4H), 7.07 (dd, *J* = 7.0 Hz, 6 Hz, 2H), 6.58 (s, 1H), 6.34 (s, 1H), 6.00 (s, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 2H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.17 (m, 1H), 4.07 (d, *J* = 12.0 Hz, 2H), 4.06 (s, 3H), 3.93 (dd, *J* = 10.5 Hz, 2 Hz, 1H), 3.85 (m, 2H), 3.68 (t, 3H, 1 H), 3.05 (dd, *J* = 10.5 Hz, 3 H, 1H).

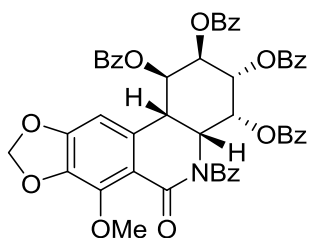
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  . 163.0 (C), 150.7 (C), 144.5 (C), 138.3 (C), 138.2 (C), 138.0 (C), 137.7 (C), 137.6 (C), 136.8 (C), 128.4 (CH x2), 128.2 (CH), 128.0 (CH), 127.8 (CH x 2), 127.7 (CH x2), 127.5 (CH), 115.8 (C), 105.3 (CH), 101.5 (CH<sub>2</sub>), 77.2 (CH), 76.9 (CH), 75.4 (CH), 75.0 (CH), 73.4 (CH<sub>2</sub> x2), 72.9 (CH<sub>2</sub>), 72.9 (CH), 70.6 (CH<sub>2</sub>), 60.9 (CH<sub>3</sub>), 50.4 (CH), 40.5 (CH).

LRMS (ESI) *m/z* 722 (M + Na).

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>43</sub>H<sub>41</sub>NNaO<sub>8</sub>, 722.2730; found, 722.2701.

IR (neat): 3411, 3086, 3062, 3029, 2926, 2850, 1659, 1608, 1475, 1454, 1496, 1475, 1454, 1396, 1350, 1267, 1216, 1094, 1053, 1026, 888, 738, 698.

**(1R,2R,3R,4R,4aR,11bS)-5-benzoyl-7-methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2,3,4-tetrayl tetrabenzoate (2-30)**



An ethyl acetate (10 mL) solution of **2-27** (147 mg, 0.210 mmol) at room temperature was treated with 20 % Pd(OH)<sub>2</sub>/C (630 mg, 0.840 mmol) and then stirred under a balloon containing H<sub>2</sub> for 9 h. At this point the reaction mixture was filtered, rinsed with MeOH and the filtrate was concentrated in vacuo to afford **2-29** (73 mg) as a white solid.

The above solid was dissolved in pyridine (1.5 mL), DMAP (6.0 mg, 0.15 mmol), and BzCl (0.40 mL, 3.4 mmol) were added to the stirred solution cooled in an ice-water bath. The mixture was stirred at room temperature for 2 h, and the reaction was quenched by the addition of H<sub>2</sub>O (10 mL). The whole was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (60 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo, and the residue was purified by

silica gel column chromatography (EtOAc/hexane 1:2) to give **2-30** (92 mg, 0.11 mmol, 50%) as a white solid of mp 115–117°C.

$[\alpha]_D^{22}$  –35.25 (*c* 1.00, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.14 (d, *J* = 7 Hz, 2H), 7.89 (d, *J* = 7 Hz, 2H), 7.70 (d, *J* = 7 Hz, 2H), 7.66 (t, *J* = 7 Hz, 2H), 7.62~7.44 (m, 7H), 7.44~7.28 (m, 9H), 7.19 (t, *J* = 8 Hz, 2H), 6.78 (t, *J* = 3 Hz, 1H), 6.40 (t, *J* = 3 Hz, 1H), 6.32 (t, *J* = 3 Hz, 1H), 6.15 (s, 1H), 6.08 (s, 1H), 5.97 (dd, *J* = 3 Hz, 1H), 5.56 (dd, *J* = 3 Hz, 1H), 4.02 (dd, *J* = 3 Hz, 1H), 3.43 (s, 3H).

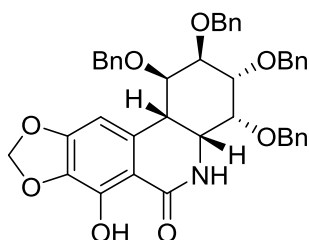
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 173 (C), 166 (C), 165 (C), 165 (C), 165 (C), 162 (C), 153 (C), 145 (C), 137 (C), 136 (C), 134 (CH), 133 (CH), 133 (C), 133 (CH), 131 (CH), 130 (CH), 130 (CH), 130 (CH), 130 (CH), 129 (CH), 128 (CH), 128 (CH), 128 (CH), 128 (CH), 128 (CH), 102 (CH<sub>2</sub>), 99 (CH), 71 (CH), 69 (CH), 69 (CH), 68 (CH), 60 (CH<sub>3</sub>), 51 (CH), 40 (CH).

LRMS (ESI) *m/z* 882 (M + Na).

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>50</sub>H<sub>37</sub>NNaO<sub>13</sub>, 882.2163; found, 882.2177.

IR (KBr): 1730, 1616, 1451, 1263, 1176, 1097, 1068, 1030, 880, 799, 712.

**(1R,2R,3R,4R,4aR,11bS)-1,2,3,4-tetrakis(benzyloxy)-7-hydroxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (2-33)**



NaI (10 mg 0.070 mmol) and TMSCl (4 v/v% in CH<sub>3</sub>CN, 0.25 mL, 0.090 mmol) were added to a stirred solution of **2-27** (50 mg, 0.070 mmol) in CH<sub>3</sub>CN (5 mL). The reaction mixture was stirred for 1 h at 60 °C and quenched by the addition of H<sub>2</sub>O at 0 °C. This was diluted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc 3:1) to give **2-33** (28 mg, 0.040 mmol, 57%) as a yellow oil.

$[\alpha]_D^{22}$  –3.95 (*c* 0.94, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 12.43 (s, 1H), 7.40~7.20 (m, 14H), 7.18 (m, 4H), 7.03 (m, 2H), 6.43 (s, 1H), 6.33 (s, 1H), 6.04 (s, 1H), 6.00 (s, 1H), 4.69 (d, *J* = 12 Hz, 1H), 4.51 (t, *J* = 12 Hz, 2H), 4.41 (t, *J* = 12 Hz, 2H), 4.44 (s, 1H), 4.40 (d, *J* = 10 Hz, 2H), 4.20 (t, *J* = 3 Hz, 1H), 4.63 (s, 2H), 3.88 (t, *J* = 3 Hz, 1H), 3.86 (t, *J* = 3 Hz, 1H), 3.82 (t, *J* = 3 Hz, 1H), 3.70 (t, *J* = 3 Hz, 1H), 3.10 (dd, *J* = 3 Hz, 10 Hz, 1H).

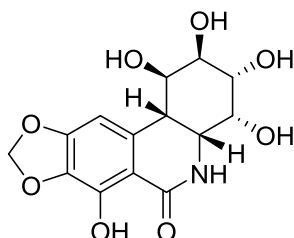
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 168 (C), 151 (C), 146 (C), 138 (C), 138 (C), 137 (C), 137 (C), 135 (C), 133 (C), 128 (CH<sub>x</sub>10), 127 (CH<sub>x</sub>10), 107 (C), 102 (CH), 102 (CH<sub>2</sub>), 76 (CH), 75 (CH), 75 (CH), 74 (CH<sub>2</sub>), 73 (CH<sub>2</sub>), 73 (CH), 73 (CH<sub>2</sub>), 71 (CH<sub>2</sub>), 51 (CH), 39 (CH).

LRMS (ESI) *m/z* 708 (M + Na).

**HRMS** (ESI) ( $m/z$ ):  $[M+Na]^+$  calcd for  $C_{42}H_{39}NNaO_8$ , 708.2573; found, 708.2555.

**IR** (neat): 3650, 3420, 3216, 1064, 3032, 2896, 1732, 1678, 1601, 1491, 1460, 1229, 1125, 1015, 838, 743, 696.

**(1*R*,2*R*,3*R*,4*R*,4*aR*,11*bS*)-1,2,3,4,7-pentahydroxy-1,3,4,4*a*,5,11*b*-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-6(2*H*)-one (2-31)**



An ethyl acetate (5 mL) solution of **2-33** (25 mg, 0.035 mmol) at room temperature was treated with 20 %  $Pd(OH)_2/C$  (100 mg, 0.140 mmol) and then stirred under a balloon containing  $H_2$  for 9 h. At this point the reaction mixture was filtered, rinsed with MeOH and the filtrate was concentrated in vacuo to afford **2-31** (9.3 mg, 0.029 mmol, 82%) as a white solid.

$[\alpha]_D^{22}$  56.76 ( $c$  0.55, MeOH).

**$^1H$  NMR** (400 MHz,  $DMSO-d_6$ ):  $\delta$  12.94 (s, 1H), 7.32 (s, 1H), 6.41 (s, 1H), 6.03 (s, 1H), 6.01 (s, 1H), 5.10 (s, 1H), 5.00 (s, 1H), 4.94 (s, 1H), 3.85 (m, 3H), 3.72 (m, 2H), 2.89 (d,  $J = 8$  Hz, 1H).

**$^1H$  NMR** (500 MHz,  $CD_3OD$ ):  $\delta$  6.44 (s, 1H), 5.99 (s, 1H), 5.98 (s, 1H), 4.09 (t,  $J = 3$  Hz, 1H), 4.03 (t,  $J = 3$  Hz, 1H), 3.99 (t,  $J = 3$  Hz, 1H), 3.94 (t,  $J = 3$  Hz, 1H), 3.93 (m, 1H), 3.00 (dd,  $J = 3$  Hz, 8 Hz, 1H).

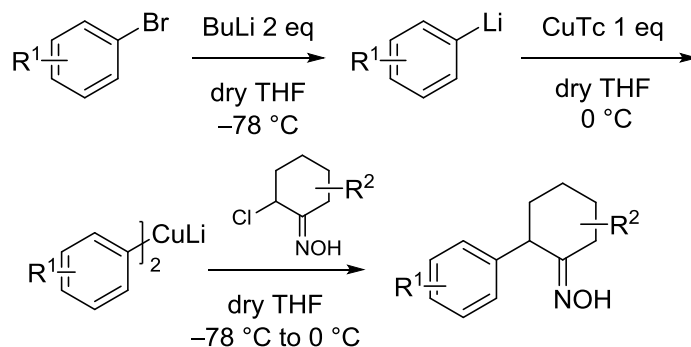
**$^{13}C$  NMR** (125 MHz,  $DMSO-d_6$ ):  $\delta$  169 (C), 151 (C), 145 (C), 137 (C), 132 (C), 107 (C), 102 ( $CH_2$ ), 102 (CH), 73 (CH), 73 (CH), 67 (CH), 67 (CH), 54 (CH), 40 (CH).

**LRMS** (ESI)  $m/z$  324 (M - H).

**HRMS** (ESI) ( $m/z$ ):  $[M-H]^+$  calcd for  $C_{14}H_{14}NO_8$ , 324.0719; found, 324.0718.

**IR** (KBr): 2907, 1719, 1677, 1470, 1355, 1278, 1218, 1084, 1030, 880, 843, 815, 778.

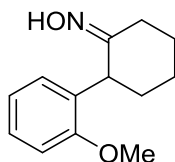
**Syntheses of Aryl oxime**



To a solution of 2-bromoanisole (0.10 mL, 0.80 mmol) in dry THF (3 mL) was added a 1.60 M hexane

solution of BuLi (0.50 mL, 0.80 mmol) dropwise at  $-78\text{ }^{\circ}\text{C}$ , and the mixture was stirred for 30 min to give a solution of the organolithium reagent. Then the mixture organolithium reagent was added to a suspension of CuTc (97 mg, 0.40 mmol) in dry THF (1 mL) at  $0\text{ }^{\circ}\text{C}$  via cannulation, and this mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 20 min to give a suspension of the diaryl cuprate. After that, the mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and added a solution of oxime **2-7** (30 mg, 0.20 mmol) in dry THF (0.5 mL+0.25 mL wash) via cannulation. Then the mixture was warmed to  $0\text{ }^{\circ}\text{C}$  and stirred for 1 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL) and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc 9:1 to 6:1 to 3:1) to give **3-6a** as a white solid.

### 2-(2-methoxyphenyl)cyclohexan-1-one oxime (**3-6a**)



Isolated yield: 84%.

**mp** 186–187  $^{\circ}\text{C}$ .

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.22 (d,  $J = 8\text{ Hz}$ , 1H), 6.82 (d,  $J = 8\text{ Hz}$ , 1H), 6.78 (s, 1H), 6.76 (dd,  $J = 2\text{ Hz}$ , 8 Hz, 1H), 3.79 (s, 3H), 3.46 (dd,  $J = 5\text{ Hz}$ , 9 Hz, 1H), 2.94 (dt,  $J = 5\text{ Hz}$ , 9 Hz, 1H), 2.14–2.26 (m, 1H), 1.95–2.10 (m, 2H), 1.72–1.90 (m, 2H), 1.52–1.68 (m, 2H).

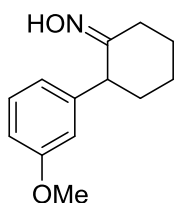
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.2 (C), 159.5 (C), 142.3 (C), 129.2 (C), 120.6 (C), 114.2 (C), 111.75 (C), 55.3 ( $\text{CH}_3$ ), 47.9 (CH), 33.0 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2$ ), 23.8 ( $\text{CH}_2$ ).

**LRMS** (ESI) ( $m/z$ ): 220 [ $\text{M} + \text{H}$ ] $^+$ .

**HRMS** (ESI) ( $m/z$ ): [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_2$ , 220.1338; found, 220.1340.

**IR** (KBr): 3267, 3064, 2998, 2938, 2845, 1714, 1671, 1598, 1492, 1461, 1324, 1240, 1132, 1047, 1031, 973, 930, 900, 756.

### 2-(3-methoxyphenyl)cyclohexan-1-one oxime (**3-6b**)



The same procedure as **3-6a** using 3-bromoanisole in place of 2-bromoanisole gave **3-6b** as a pale yellow solid. Isolated yield: 71%.

**mp** 119–120 $^{\circ}\text{C}$ .

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.21 (d,  $J = 8\text{ Hz}$ , 2H), 6.96 (d,  $J = 8\text{ Hz}$ , 1H), 6.88 (d,  $J = 8\text{ Hz}$ , 1H),

3.87 (dd,  $J = 12$  Hz, 1H), 3.80 (s, 3H), 3.40 (dd,  $J = 4$  Hz, 12 Hz, 1H), 1.87–1.97 (m, 5H), 1.50–1.70 (m, 2H).

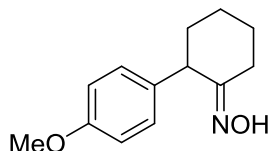
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.1 (C), 156.7 (C), 129.4 (C), 128.5 (C), 127.6 (C), 120.4 (C), 110.6 (C), 55.5 ( $\text{CH}_3$ ), 41.4 (CH), 33.0 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ).

LRMS (ESI) ( $m/z$ ): 220 [ $\text{M} + \text{H}$ ] $^+$ .

HRMS (ESI) ( $m/z$ ): [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_2$ , 220.1338; found, 220.1351.

IR (KBr): 3201, 2931, 2833, 1662, 1609, 1583, 1488, 1446, 1262, 1051, 966, 926, 771, 745, 700.

### 2-(4-methoxyphenyl)cyclohexan-1-one oxime (3-6c)



The same procedure as **3-6a** using 4-bromoanisole in place of 2-bromoanisole gave **3-6c** as a pale yellow solid.

Isolated yield: 73%. mp 165–166 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (d,  $J = 8$  Hz, 2H), 6.86 (d,  $J = 8$  Hz, 2H), 3.79 (s, 3H), 3.45 (t,  $J = 7$  Hz, 1H), 3.01 (t,  $J = 7$  Hz, 1H), 2.12–2.22 (m, 1H), 1.98–2.06 (m, 2H), 1.80–1.88 (m, 2H), 1.56–1.64 (m, 2H).

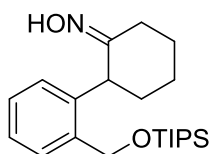
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.8 (C), 158.1 (C), 132.7 (C), 129.1 (Cx2), 113.7 (Cx2), 55.2 ( $\text{CH}_3$ ), 47.2 (CH), 33.4 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 23.9 ( $\text{CH}_2$ ).

LRMS (ESI) ( $m/z$ ): 220 [ $\text{M} + \text{H}$ ] $^+$ .

HRMS (ESI) ( $m/z$ ): [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_2$ , 220.1338; found, 220.1328.

IR (KBr): 3193, 2939, 2835, 1667, 1611, 1514, 1461, 1441, 1248, 1037, 970, 924, 841, 809, 778, 754.

### 2-(2-(((triisopropylsilyl)oxy)methyl)phenyl)cyclohexan-1-one oxime (3-6e)



Analogous procedure as **3-6a** gave **3-6e** as a white solid. Isolated yield: 64%.

mp 122–123 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (d,  $J = 8$  Hz, 1H), 7.20–7.25 (m, 3H), 4.81 (d,  $J = 12$  Hz, 1H), 4.62 (d,  $J = 12$  Hz, 1H), 3.76 (dd,  $J = 4$  Hz, 12 Hz, 1H), 3.40 (d,  $J = 13$  Hz, 1H), 2.65 (d,  $J = 8$  Hz, 1H), 1.94 (d,  $J = 12$  Hz, 2H), 1.75 (t,  $J = 13$  Hz, 1H), 1.48–1.66 (m, 3H), 1.07 (d,  $J = 3$  Hz, 18H), 1.05 (d,  $J = 3$  Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.0 (C), 145.8 (C), 138.7 (C), 127.7 (CH), 127.6 (CH), 127.1 (CH), 126.5 (CH), 63.9 ( $\text{CH}_2$ ), 44.0 (CH), 33.7 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 18.1 ( $\text{CH}_3$  x6), 12.0 (CH x3).

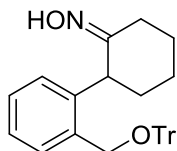


**LRMS** (ESI) ( $m/z$ ): 388  $[M+Na]^+$ .

**HRMS** (ESI) ( $m/z$ ):  $[M+Na]^+$  calcd for  $C_{22}H_{37}NO_2SiNa$ , 398.2491; found, 398.2491.

**IR** (KBr): 3278, 3179, 3089, 2946, 2866, 2716, 1461, 1360, 1252, 1079, 1038, 1013, 993, 881, 747, 672, 638.

### 2-(2-(((trityl)oxy)methyl)phenyl)cyclohexan-1-one oxime (3-6f)



Analogous procedure as **3-6a** gave **3-6f** as a white solid. Isolated yield: 65%.

**mp** 212–213 °C.

**<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  6.43 (s, 1H), 6.38 (s, 1H), 5.99 (s, 2H), 3.86 (s, 3H), 3.37 (dd,  $J = 9.0, 5.5$  Hz, 1H), 3.00 (dt,  $J = 14.0, 4.0$  Hz, 1H), 2.10 (m, 1H), 2.04–1.90 (m, 2H), 1.90–1.70 (m, 2H), 1.70–1.50 (m, 2H).

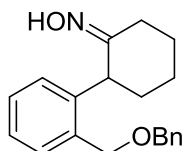
**<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  162.2 (C), 148.8 (C), 143.4 (C), 135.2 (C), 133.8 (C), 107.9 (CH), 102.4 (CH), 101.3 ( $CH_2$ ), 56.6 ( $CH_3$ ), 48.1 (CH), 33.5 ( $CH_2$ ), 25.7 ( $CH_2$ ), 24.8 ( $CH_2$ ), 24.0 ( $CH_2$ ).

**LRMS** (ESI) ( $m/z$ ): 262  $[M-H]^-$ .

**HRMS** (ESI) ( $m/z$ ):  $[M-H]^-$  calcd for  $C_{14}H_{16}NO_4$ , 262.1079; found, 262.1089.

**IR** (KBr): 3276, 3057, 3029, 2934, 2864, 1961, 1823, 1736, 1491, 1446, 1379, 1316, 1217, 1057, 983, 929, 901, 769, 747, 705.

### 2-(2-(((Benzyl)oxy)methyl)phenyl)cyclohexan-1-one oxime (3-6g)



Analogous procedure as **3-6a** gave **3-6g** as a white solid. Isolated yield: 66%.

**mp** 149–150 °C.

**<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  7.28–7.38 (m, 8H), 7.22 (dt,  $J = 7.0, 2.5$  Hz, 1H), 6.80–6.90 (br, 1H), 4.55 (t,  $J = 12.0$  Hz, 2H), 4.47 (d,  $J = 12.0$  Hz, 1H), 4.42 (d,  $J = 12.0$  Hz, 1H), 3.72 (dd,  $J = 12.0, 4.5$  Hz, 1H), 3.38 (d,  $J = 14.0$  Hz, 1H), 2.00–2.10 (m, 1H), 1.90–1.98 (m, 3H), 1.67 (dt,  $J = 14.0, 4.5$  Hz, 1H), 1.55–1.45 (m, 2H).

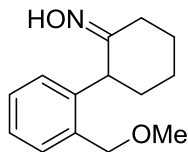
**<sup>13</sup>C NMR** (101 MHz,  $CDCl_3$ ):  $\delta$  162.4 (C), 140.1 (C), 138.3 (C), 135.2 (C), 129.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 126.5 (CH), 72.1 ( $CH_2$ ), 70.6 ( $CH_2$ ), 44.2 (CH), 33.8 ( $CH_2$ ), 26.0 ( $CH_2$ ), 25.7 ( $CH_2$ ), 24.7 ( $CH_2$ ).

**LRMS** (ESI) ( $m/z$ ): 348  $[M+K]^+$ .

**HRMS** (ESI) ( $m/z$ ):  $[M+K]^+$  calcd for  $C_{20}H_{23}NO_2K$ , 348.1366; found, 348.1378.

**IR** (KBr): 3223, 3062, 3036, 2925, 2867, 1493, 1450, 1410, 1360, 1102, 1071, 1022, 978, 934, 903, 745, 696.

### 2-(2-(((methyl)oxy)methyl)phenyl)cyclohexan-1-one oxime (3-6h)



Analogous procedure as **3-6a** gave **3-6h** as a white solid. Isolated yield: 67%.

**mp** 139–140 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.28–7.33 (m, 3H), 7.24 (d, *J* = 4.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.76 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.46 (dt, *J* = 14.0, 3.5 Hz, 1H), 3.34 (s, 3H), 1.88–2.10 (m, 1H), 1.90–2.04 (m, 3H), 1.85 (dt, *J* = 14.0, 4.0 Hz, 1H), 1.65 (dt, *J* = 12.0, 4.0 Hz, 1H), 1.50–1.60 (m, 1H).

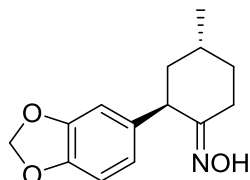
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 162.3 (C), 139.8 (C), 135.2 (C), 135.7 (C), 129.31 (CH), 128.0 (CH), 127.9 (CH), 73.1 (CH<sub>2</sub>), 58.0 (CH<sub>3</sub>), 44.3 (CH), 33.8 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 24.8 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 272 [M+K]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+K]<sup>+</sup> calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>K, 272.1053; found, 272.1047.

**IR** (KBr): 3414, 3256, 2927, 2867, 2827, 1667, 1488, 1443, 1360, 1216, 1183, 1080, 975, 931, 903, 788.

### 2-(benzo[d][1,3]dioxol-5-yl)-4-methylcyclohexan-1-one oxime (3-6k)



Analogous procedure as **3-6a** gave **3-6k** as a white solid. Isolated yield: 46%.

**mp** 101–102 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.70–6.80 (m, 3H), 5.96 (s, 2H), 3.67 (t, *J* = 4 Hz, 1H), 3.09 (dt, *J* = 14.0, 4.0 Hz, 1H), 2.32 (dt, *J* = 14.0, 4.0 Hz, 1H), 1.82–2.00 (m, 2H), 1.74–1.82 (m, 1H), 1.50–1.60 (m, 1H), 1.26 (t, *J* = 7 Hz, 1H), 0.97 (d, *J* = 6.0, 3H).

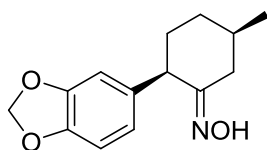
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 162.2 (C), 147.8 (C), 145.9 (C), 134.5 (C), 120.4 (CH), 108.2 (CH), 108.0 (CH), 100.9 (CH<sub>2</sub>), 43.6 (CH), 38.7 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 27.1 (CH), 21.3 (CH<sub>3</sub>), 21.3 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 270 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>3</sub>, 248.1287; found, 248.1286.

**IR** (KBr): 3252, 3119, 3072, 2954, 2925, 2886, 2778, 1846, 1713, 1667, 1503, 1450, 1369, 1246, 1229, 1040, 935, 772, 680.

### 2-(benzo[d][1,3]dioxol-5-yl)-4-methylcyclohexan-1-one oxime (3-6l)



Analogous procedure as **3-6a** gave **3-6l** as a white solid. Isolated yield: 56%.

**mp** 144–145 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.72–6.78 (m, 3H), 5.93 (s, 2H), 3.56 (t, *J* = 4 Hz, 1H), 2.93 (q, *J* = 9.5, 1H), 2.35 (dt, *J* = 14.0, 5.0 Hz, 1H), 1.65–1.70 (m, 1H), 1.32–1.46 (m, 1H), 0.96 (d, *J* = 5 Hz, 3H).

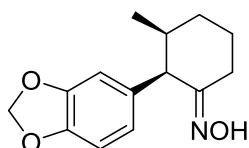
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 162.1 (C), 147.9 (C), 146.0 (C), 134.3 (C), 120.6 (C), 108.3 (CH), 108.2 (CH), 101.0 (CH<sub>2</sub>), 44.4 (CH), 32.3 (CH), 30.4 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>).

**LRMS** (ESI) (*m/z*): 270 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>Na, 270.1106; found, 270.1095.

**IR** (KBr): 3269, 3078, 2952, 2888, 2789, 1863, 1736, 1658, 1634, 1502, 1438, 1248, 1041, 938, 871, 813, 771.

### 2-(benzo[d][1,3]dioxol-5-yl)-3-methylcyclohexan-1-one oxime (3-6m)



Analogous procedure as **3-6a** gave **3-6f** as a white solid. Isolated yield: 40%.

**mp** 131–132 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.75 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 5.59 (d, *J* = 8.0 Hz, 1H), 5.93 (d, *J* = 2.5 Hz, 2H), 3.34 (d, *J* = 15.0 Hz, 1H), 2.88 (d, *J* = 11 Hz, 1H), 1.94–1.91 (m, 3H), 1.77 (dt, *J* = 13.0, 4.0 Hz, 1H), 1.60–1.50 (m, 4H), 1.32 (dt, *J* = 13.0, 4.0 Hz, 1H), 0.77 (d, *J* = 6.0 Hz, 3H).

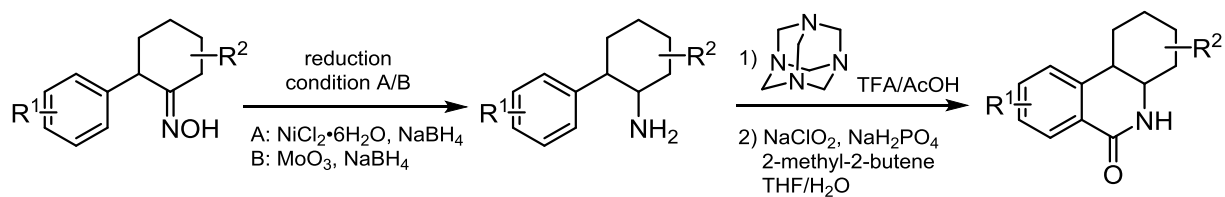
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 162.4 (C), 147.5 (C), 146.1 (C), 133.2 (C), 122.3 (C), 109.2 (CH), 108.0 (CH), 100.8 (CH<sub>2</sub>), 56.1 (CH), 38.5 (CH), 34.3 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 20.7 (CH<sub>3</sub>).

**LRMS** (ESI) (*m/z*): 270 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>3</sub>, 248.1287; found, 248.1283.

**IR** (KBr): 3262, 3115, 2927, 2890, 2845, 2775, 1864, 1703, 1667, 1489, 1442, 1241, 939, 810, 772.

### Procedure of lactam formation 1)



### **Procedure A**

A 20 mL flask was charged with oxime (0.196 mmol) EtOH (3.0 mL) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (132 mg, 0.392 mmol). To the mixture cooled in an ice–water bath,  $\text{NaBH}_4$  (106 mg, 2.85 mmol) was portion-wise added, and the cooling bath was removed. After 1.5 h, the mixture was cooled in an ice–water bath,  $\text{NaBH}_4$  (106 mg, 2.85 mmol) was portion-wise added again. The mixture was stirred at rt for 2 h and diluted with EtOAc (20 mL). After addition of  $\text{H}_2\text{O}$  (20 mL), the whole was filtered through celite pad, which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to give crude amine. Cis- and trans- amine were separated by silica gel column chromatography (hexane/EtOAc 3:1 to EtOAc only to EtOAc/EtOH 1:2).

To a solution of amine **2-25** (106 mg, 0.15 mmol) in AcOH:TFA (2.4 mL, 3:1) at room temperature was added hexamethylenetetramine (112 mg, 0.75 mmol) and the resulting mixture was heated to 90 °C and stirred for 5 h until complete conversion. The reaction mixture was concentrated under reduced pressure and dissolved in MeOH (10 mL) and  $\text{NaHCO}_3$  (4.8 g) was carefully added. The mixture was then loaded onto Celite pad which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  (20 mL) and brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to give crude imine which was purified by silica gel column chromatography (hexane/EtOAc 1:2) to give the corresponding imine.

To a solution of imine (0.11 mmol) in THF (1.1 mL) were added 2-methyl-2-butene (0.64 mL, 5.5 mmol), water (1.1 mL),  $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$  (246 mg, 2.20 mmol), and  $\text{NaClO}_2$  (330 mg, 2.20 mmol) at 0 °C. The mixture was warmed to room temperature slowly in an ice–water bath. Then, saturated aqueous  $\text{Na}_2\text{SO}_3$  (5 mL) was added, and the whole was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound.

### **Procedure B**

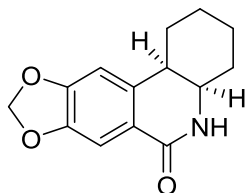
A 20 mL flask was charged with oxime (0.06 mmol) MeOH (1.0 mL) and  $\text{MoO}_3$  (13 mg, 0.09 mmol). To the mixture cooled in an ice–water bath,  $\text{NaBH}_4$  (11 mg, 0.30 mmol) was portion-wise added. After stirring at this temperature for 1 h,  $\text{MoO}_3$  (13 mg, 0.09 mmol) and  $\text{NaBH}_4$  (11 mg, 0.30 mmol) was portion-wise added again. The mixture was stirred at rt for 2 h and diluted with EtOAc (5 mL). After addition of  $\text{H}_2\text{O}$  (5 mL), the whole was filtered through celite pad, which was successively washed with EtOAc (10 mL x3). The combined organic layers were washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to give crude amine. Cis- and trans- amine were

separated by silica gel column chromatography (hexane/EtOAc 3:1 to EtOAc only to EtOAc/EtOH 1:2).

To a solution of amine (0.15 mmol) in AcOH:TFA (2.4 mL, 3:1) at room temperature was added hexamethylenetetramine (112 mg, 0.75 mmol) and the resulting mixture was heated to 90 °C and stirred for 5 h until complete conversion. The reaction mixture was concentrated under reduced pressure and dissolved in MeOH (10 mL) and NaHCO<sub>3</sub> (4.8 g) was carefully added. The mixture was then loaded onto Celite pad which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give crude imine which was purified by silica gel column chromatography (hexane/EtOAc 1:2) to give corresponding imine.

To a solution of imine (0.11 mmol) in THF (1.1 mL) were added 2-methyl-2-butene (0.64 mL, 5.5 mmol), water (1.1 mL), NaH<sub>2</sub>PO<sub>4</sub>•2H<sub>2</sub>O (246 g, 2.20 mmol), and NaClO<sub>2</sub> (330 mg, 2.20 mmol) at 0 °C. The mixture was warmed to roomtemperature slowly in an ice–water bath. Then, saturated aqueous Na<sub>2</sub>SO<sub>3</sub> (5 mL) was added, and the whole was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound.

#### **Cis-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (*cis*-3-8a)**



Decomposes above 250 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.52 (s, 1H), 6.64 (s, 1H), 5.99 (dd, *J* = 4.0, 1.5 Hz, 2H), 5.37 (br, 1H), 3.88 (dd, *J* = 7.0, 4.0 Hz, 1H), 2.65–5.75 (m, 1H), 1.70–1.80 (m, 2H), 1.50–1.65 (m, 4H), 1.40–1.30 (m, 1H).

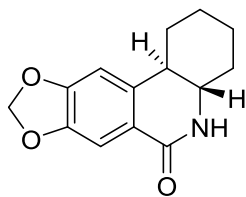
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 168.2 (C), 151.0 (C), 146.8 (C), 121.6 (C), 108.0 (CH), 106.7 (CH), 101.5 (CH<sub>2</sub>), 50.1 (CH<sub>3</sub>), 40.3 (CH), 30.2 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 19.8 (CH<sub>2</sub>).

LRMS (ESI) (*m/z*): 268 [M+Na]<sup>+</sup>.

HRMS (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>Na, 268.0947; found, 268.0958.

IR (KBr): 3173, 3054, 2936, 2857, 1668, 1493, 1458, 1412, 1388, 1359, 1322, 1262, 1241, 1037, 934, 807, 741.

#### **Trans-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (*trans*-3-8a)**



**mp** 191–192 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.54 (s, 1H), 6.76 (s, 1H), 6.01 (s, 2H), 5.57 (s, 2H), 3.22 (dt, *J* = 11.0, 4.0 Hz, 1H), 2.62 (dt, *J* = 11.0, 4 Hz, 1H), 2.34 (d, *J* = 12.0 Hz, 1H), 1.83–1.98 (m, 3H), 1.25–1.55 (m, 4H).

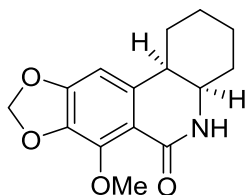
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 165.6 (C), 151.2 (C), 146.5 (C), 138.2 (C), 123.3 (C), 108.2 (CH), 103.9 (CH), 101.5 (CH<sub>2</sub>), 55.8 (CH<sub>3</sub>), 42.0 (CH), 32.2 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 268 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>Na, 268.0947; found, 268.0950.

**IR** (KBr): 3278, 3052, 2935, 2860, 1668, 1503, 1460, 1389, 1361, 1255, 1033, 930, 771.

**Cis-7-methoxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (*cis*-3-8b)**



**mp** 189–190 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.39 (s, 1H), 5.97 (d, *J* = 12.0 Hz, 2H), 5.34 (br, 1H), 4.05 (s, 3H), 3.79 (dd, *J* = 6.5, 3.0 Hz, 1H), 2.56–2.63 (m, 1H), 1.70–1.82 (m, 2H), 1.52–1.68 (m, 4H), 1.24–1.40 (m, 2H).

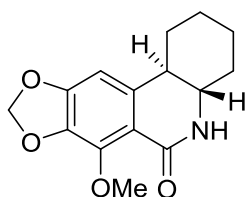
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 164.6 (C), 151.5 (C), 144.9 (C), 141.8 (C), 137.1 (C), 114.5 (C), 101.9 (CH), 101.4 (CH<sub>2</sub>), 60.8 (CH<sub>3</sub>), 49.1 (CH), 41.9 (CH), 29.7 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 19.6 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 298 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>NO<sub>4</sub>, 276.1236; found, 276.1222.

**IR** (KBr): 3549, 3480, 3411, 3050, 2941, 2898, 2878, 2842, 1670, 1474, 1388, 1357, 1322, 1217, 1061, 1040, 941, 807, 775.

**Trans-7-methoxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2H)-one (*trans*-3-8b)**



mp 204–205 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 6.50 (s, 1H), 5.98 (d, *J* = 12.0 Hz, 2H), 5.62 (br, 1H), 4.06 (s, 3H), 3.10 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.50 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.28 (d, *J* = 12.0 Hz, 1H), 1.87–1.97 (m, 2H), 1.81–1.87 (m, 1H), 1.36–1.46 (m, 2H), 1.22–1.34 (m, 2H).

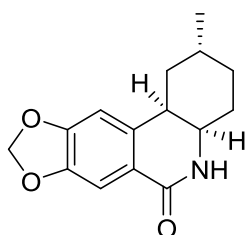
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 163.9 (C), 151.7 (C), 148.6 (C), 139.9 (C), 136.8 (C), 105.8 (C), 101.4 (CH<sub>2</sub>), 99.0 (CH), 60.8 (CH<sub>3</sub>), 54.7 (CH), 43.0 (CH), 31.8 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 298 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>NO<sub>4</sub>, 276.1236; found, 276.1235.

**IR** (KBr): 3182, 3060, 2926, 2855, 1729, 1663, 1509, 1475, 1363, 1325, 1278, 1217, 1136, 1088, 1035, 927, 797, 769, 727, 630.

**Cis-2-methyl-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-6(2H)-one** (*cis*-3-8c)



mp 237–238 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.54 (s, 1H), 6.71 (s, 1H), 6.00 (s, 2H), 5.76 (br, 1H), 3.60 (q, *J* = 4.0 Hz, 1H), 2.12 (d, *J* = 12.0 Hz, 1H), 1.65–1.83 (m, 3H), 1.34–1.44 (ddd, *J* = 14.0, 4.0 Hz, 1H), 1.26 (t, *J* = 6.5 Hz, 1H), 1.06–1.18 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H).

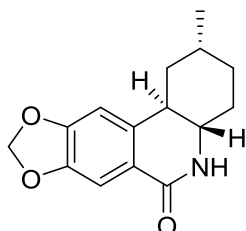
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>): δ 165.4 (C), 151.3 (C), 146.5 (C), 137.3 (C), 122.5 (C), 108.3 (CH), 106.0 (CH), 101.5 (CH<sub>2</sub>), 51.8 (CH), 36.1 (CH), 35.1 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 27.6 (CH), 26.1 (CH<sub>2</sub>), 20.1 (CH<sub>3</sub>).

**LRMS** (ESI) (*m/z*): 282 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub>Na, 282.1106; found, 282.1093.

**IR** (KBr): 3182, 3057, 2901, 2870, 2784, 1667, 1503, 1458, 1388, 1245, 1039, 934, 900, 860, 797, 773, 686.

**Trans-2-methyl-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-6(2H)-one** (*trans*-3-8c)



mp 237–238 °C.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.54 (s, 1H), 6.76 (s, 1H), 6.01 (s, 2H), 5.57 (s, 2H), 3.22 (dt, *J* = 11.0, 4.0 Hz, 1H), 2.62 (dt, *J* = 11.0, 4 Hz, 1H), 2.34 (d, *J* = 12.0 Hz, 1H), 1.83–1.98 (m, 3H), 1.25–1.55 (m,

4H).

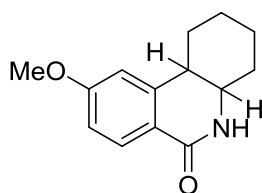
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.6 (C), 151.2 (C), 146.5 (C), 138.2 (C), 123.3 (C), 108.2 (CH), 103.9 (CH), 101.5 ( $\text{CH}_2$ ), 55.8 ( $\text{CH}_3$ ), 42.0 (CH), 32.2 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 24.1 ( $\text{CH}_2$ ).

LRMS (ESI) ( $m/z$ ): 282 [ $\text{M}+\text{Na}$ ] $^+$ .

HRMS (ESI) ( $m/z$ ): [ $\text{M}+\text{Na}$ ] $^+$  calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}$ , 282.1106; found, 282.1110.

IR (KBr): 3554, 3480, 3414, 3181, 3146, 3055, 2944, 2870, 1671, 1502, 1471, 1455, 1382, 1252, 1037, 934, 887, 815, 773, 638.

### 9-methoxy-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2H)-one (3-8d)



Mixture of *cis*-3-8d/*trans*-3-8d = 1:1.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (d,  $J$  = 8.0 Hz, 1H), 8.02 (d,  $J$  = 8.0 Hz, 1H), 6.86 (d,  $J$  = 2.5 Hz, 1H), 6.84 (d,  $J$  = 8.0 Hz, 1H), 6.78 (s, 1H), 6.69 (d,  $J$  = 2.5 Hz, 1H), 6.04 (br, 1H), 5.80 (br, 1H), 3.90 (q,  $J$  = 3.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.27 (dt,  $J$  = 11.0, 4.0 Hz, 1H), 2.74 (m, 1H), 2.67 (dt,  $J$  = 11.0, 4 Hz, 1H), 2.38 (dd,  $J$  = 12.0, 3.0 Hz, 1H), 1.91–1.98 (m, 2H), 1.77–1.91 (m, 3H), 1.55–1.76 (m, 5H), 1.22–1.46 (m, 5H).

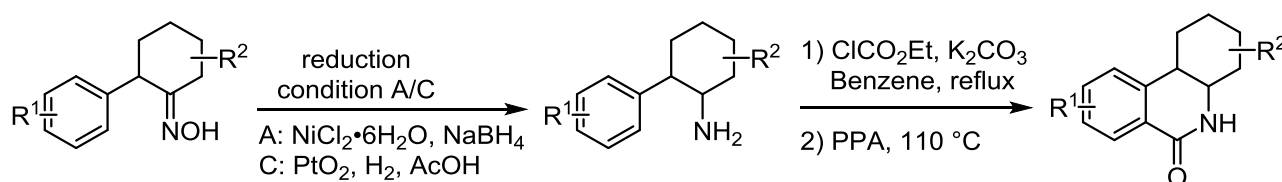
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7 (C), 166.0 (C), 163.0 (C), 162.8 (C), 130.3 (C), 130.3 (C), 122.0 (CH), 120.5 (CH), 112.2 (CH), 111.9 (CH), 111.2 (CH), 109.6 (CH), 55.6 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 50.1 (CH), 42.2 (CH), 40.5 (CH), 32.3 (CH), 30.2 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2$ ), 24.1 ( $\text{CH}_2$ ), 19.9 ( $\text{CH}_2$ ).

LRMS (ESI) ( $m/z$ ): 254 [ $\text{M}+\text{Na}$ ] $^+$ .

HRMS (ESI) ( $m/z$ ): [ $\text{M}+\text{H}$ ] $^+$  calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$ , 232.1338; found, 232.1334.

IR (KBr): 3182, 3063, 3002, 2931, 2853, 1659, 1604, 1539, 1496, 1463, 1442, 1392, 1355, 1322, 1269, 1255, 1172, 1151, 1098, 1033, 845, 807, 770.

### Procedure of lactam formation 2)



### Procedure C

A 20 mL flask was charged with oxime (0.196 mmol) EtOH (3.0 mL) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (132 mg, 0.392 mmol). To the mixture cooled in an ice–water bath,  $\text{NaBH}_4$  (106 mg, 2.85 mmol) was portion-



wise added, and the cooling bath was removed. After 1.5 h, the mixture was cooled in an ice–water bath, NaBH<sub>4</sub> (106 mg, 2.85 mmol) was portion-wise added again. The mixture was stirred at rt for 2 h and diluted with EtOAc (20 mL). After addition of H<sub>2</sub>O (20 mL), the whole was filtered through celite pad, which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give crude amine. Cis- and trans- amine were separated by silica gel column chromatography (hexane/EtOAc 3:1 to EtOAc only to EtOAc/EtOH 1:2).

To the above amine (0.055 mmol) in benzene (1.0 mL) was added anhydrous potassium carbonate (12 mg, 0.082 mmol) and ethyl chloroformate (0.015 mL, 0.14 mmol) and the mixture was refluxed for 1 h. Filtration and removal of benzene in vacuo gave a thick oil which solidified on addition hexane. Recrystallization from hexane/EtOAc 4:1 gave the corresponding carbamate.

The above carbamate (0.043 mmol) and PPA (200 mg) were heated at 110 °C. After 1.5 h, the mixture was treated with 5 mL water and filtered. The residue was purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound.

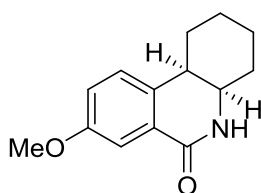
#### **Procedure D**

A 20 mL flask was charged with oxime (0.08 mmol) AcOH (1.0 mL).and PtO<sub>2</sub> (1.8 mg, 0.008 mmol) at room temperature. The mixture was stirred under a balloon containing H<sub>2</sub> for 6 h. At this point the reaction mixture was filtered, rinsed with MeOH and the filtrate was concentrated in vacuo. Then the obtained mixture was diluted with EtOAc (10 mL) and added 2 M NaOH aqueous solution until pH = 12. The whole was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (20 mLx2), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1 to EtOAc only to EtOAc/EtOH 1:2) to give the corresponding amine.

To the above amine (0.055 mmol) in benzene (1.0 mL) was added anhydrous potassium carbonate (12 mg, 0.082 mmol) and ethyl chloroformate (0.015 mL, 0.14 mmol) and the mixture was refluxed for 1 h. Filtration and removal of benzene in vacuo gave a thick oil which solidified on addition hexane. Recrystallization from hexane/EtOAc 4:1 gave the corresponding carbamate.

The above carbamate (0.043 mmol) and PPA (200 mg) were heated at 110 °C. After 1.5 h, the mixture was treated with 5 mL water and filtered. The residue was purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound.

#### **(4aR,10bR)-8-methoxy-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2H)-one (*cis*-3-8f)**



Procedure C gave *cis*-**3-8f** as a white solid. **mp** 177–178 °C.

**H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.60 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H), 5.60 (br, 1H), 3.90 (d, *J* = 3.0 Hz, 1H), 3.85 (s, 3H), 2.70–2.80 (m, 1H), 1.50–1.80 (m, 5H), 1.30–1.45 (m, 1H), 1.25 (s, 2H).

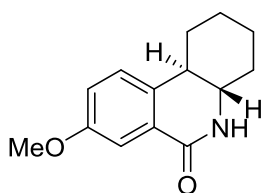
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 166.7 (C), 158.6 (C), 140.4 (C), 128.6 (C), 128.0 (CH), 120.2 (CH), 111.1 (CH), 55.7 (CH<sub>3</sub>), 50.3 (CH), 39.4 (CH), 30.3 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 19.9 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 254 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>Na, 254.1157; found, 232.1161.

**IR** (KBr): 3051, 2930, 2895, 1737, 1666, 1493, 1453, 1390, 1321, 1270, 1250, 1037, 804, 771.

(4a*S*,10b*R*)-8-methoxy-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2H)-one (*trans*-**3-8f**)



Procedure C gave *trans*-**3-8f** as a white solid. **mp** 194–195 °C.

**H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.61 (d, *J* = 3.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0 Hz, 3.0 Hz, 1H), 5.91 (br, 1H), 3.85 (s, 3H), 3.24 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.65 (dt, *J* = 12.0, 4.0 Hz, 1H), 2.341 (dd, *J* = 12.0, 3.0 Hz, 1H), 1.83–1.98 (m, 3H), 1.25–1.60 (m, 4H).

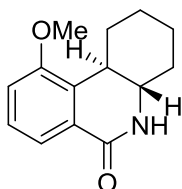
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 166.0 (C), 158.5 (C), 134.5 (C), 130.2 (C), 124.7 (CH), 119.6 (CH), 111.5 (CH), 56.0 (CH<sub>3</sub>), 41.6 (CH), 32.2 (CH), 29.9 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 254 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>2</sub>, 232.1338; found, 232.1334.

**IR** (KBr): 3191, 3066, 2968, 2872, 2833, 1668, 1494, 1429, 1357, 1313, 1261, 1030, 877, 801, 774, 724, 673.

(4a*S*,10b*R*)-10-methoxy-1,3,4,4a,5,10b-hexahydrophenanthridin-6(2H)-one (*trans*-**3-8g**)



Procedure D gave *trans*-**3-8g** as a white solid. **mp** 225–226 °C.

**H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.32 (dq, *J* = 11.5, 3.5 Hz, 2H), 2.81 (dt, *J* = 11.5, 3.5 Hz, 1H), 1.83–1.98 (m, 3H), 1.20–1.50 (m, 4H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 166.3 (C), 158.0 (C), 131.2 (C), 130.2 (C), 127.6 (CH), 121.1 (CH),

116.0 (CH), 55.8 (CH<sub>3</sub>), 43.1 (CH), 33.0 (CH), 29.8 (CH<sub>2</sub>), 28.1 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>).

**LRMS** (ESI) (*m/z*): 254 [M+Na]<sup>+</sup>.

**HRMS** (ESI) (*m/z*): [M+K]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>K, 270.0896; found, 270.0901.

**IR** (KBr): 3182, 3073, 2928, 2857, 1674, 1573, 1494, 1462, 1405, 1256, 1050, 815, 755.

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