海洋産アルカロイド

ナカドマリン Aの不斉全合成と絶対構造の決定

2003年

長田 敏明

海洋産アルカロイド

ナカドマリン Aの不斉全合成と絶対構造の決定

2003年

長田 敏明

海洋産アルカロイド ナカドマリンAの不斉全合成と絶対構造の決定

目次

略語

略語

本論文中以下の略語を用いた。

Ac: acetyl

AIBN: 2,2'-azabisisobutyronitrile

9-BBN: 9-borabicyclo[3.3.1]nonane

Bn: benzyl

Boc: *t*-butoxycarbonyl

BOP: benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate

Bs: benzenesulfonyl

Bu: butyl

Bz: benzoyl

CAN: ceric ammonium nitrate

CDK4: cyclin dependent kinase 4

COSY: correlation spectroscopy

CSA: (1*S*)-(+)-10-camphorsulfonic acid

Cy: cyclohexyl

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DEPT: distortionless enhancement by polarization transfer

DHP: dihydropyran

DIBAL-H: diisobutylaluminium hydride

DMAP: 4-(dimethylamino)pyridine

DME: 1,2-dimethoxyethane

DMF: *N,N*-dimethylformamide

DMSO: dimethyl sulfoxide

DPPF: 1,1'-bis(diphenylphosphino) ferrocene

Et: ethyl

HMBC: ^{1}H-detected multiple-bond hetero nuclear multiple quantum coherence spectrum

HMPA:hexamethylphosphorous triamide

HOBt: 1-hydroxybenzotriazole

HPLC: high performance liquid chromatography

KHMDS: Potassium hexamethyldisilazane

LDA: Lithium diisopropylamide

LiHMDS:Lithium hexamethyldisilazane

*m*CPBA: *m*-chloroperbenzoic acid

Me: methyl

Mes: 2,4,6-trimethylphenyl

NMO: 4-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

nOe: nuclear Overhauser effect

NOESY: nOe spectroscopy

PEA: phenylethylamine

Ph: phenyl

PMB: *p*-methoxybenzyl

PMBz: *p*-methoxybenzoyl

PPTS: pyridinium *p*-toluenesulfonate

Pr: propyl

RCM: ring closing metathesis

Red-Al: sodium bis(2-methoxyethoxy) aluminium hydride

TBAF: tetrabutylammonium fluoride

TBS: *t*-butyl dimethylsilyl

TBDPS: *t*-butyl diphenylsilyl

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

THF: tetrahydrofuran

THP: tetrahydropyranyl

TLC: thin-layer chromatography

TMS: tetramethylsilane, trimethylsilyl

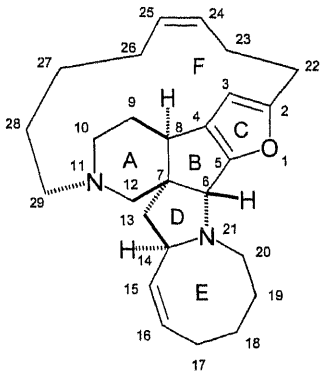
TsOH: *p*-toluenesulfonic acid

WSC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

序論

ナカドマリンA (1)[1] (Fig. 1, 以下、ナンバリングはナカドマリンAに従った)は、小林らにより1997年に沖縄産海綿 [*Amphimedon sp.* (SS-264)]から単離構造決定された抗腫瘍・抗菌性マンザミン関連アルカロイド[2]である。ナカドマリンA (1)は、抗腫瘍活性 L1210 (IC_{50} 1.3 μg/ml), 細胞毒性 CDK4阻害活性(IC_{50} 9.9 μg/ml)を示すものの、単離量(湿海綿重量の0.0018%)が少なく、充分な活性の評価がなされていない。ナカドマリンA (1)はフラン環を含む8/5/5/5/15/6という高度に縮合した複雑な6環性構造を有する光学活性体であるが、絶対配置は未決定である。その構造は合成的見地からも興味深く、これまでに我々以外に4例のモデル合成[3]が報告されたが全合成の報告はない。そこで我々はマンザミン関連アルカロイドの合成研究[2]をふまえ、ナカドマリンA (1)の絶対配置の決定と供給法の確立を目的に2000年に全合成研究に着手した。

Fig. 1

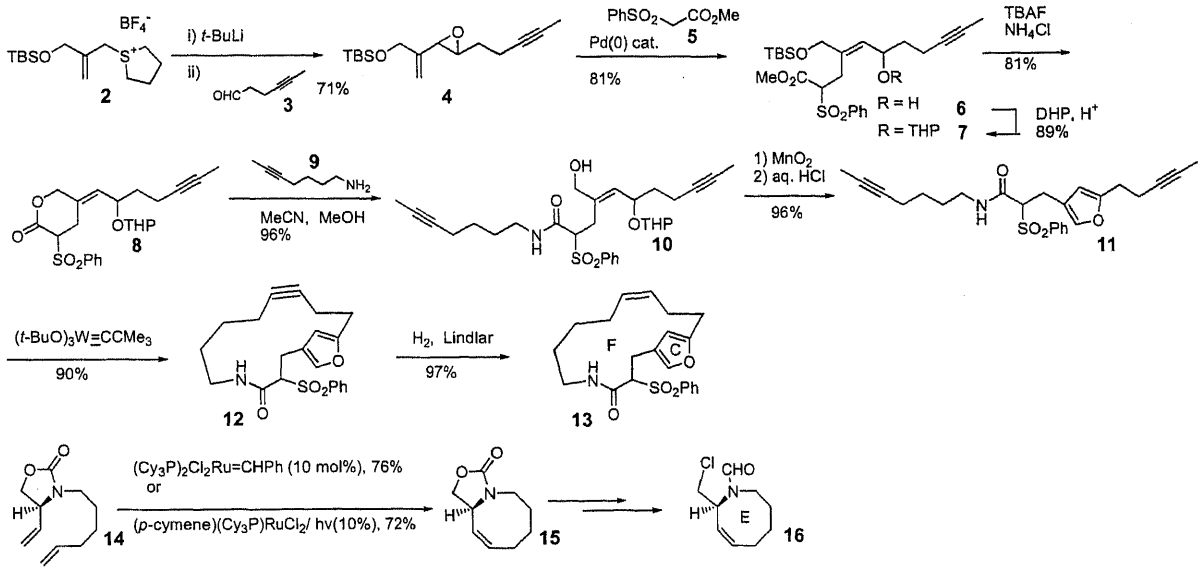


Nakadomarin A (1)

まず、ナカドマリンA (1)のモデル合成(4例)を示す。

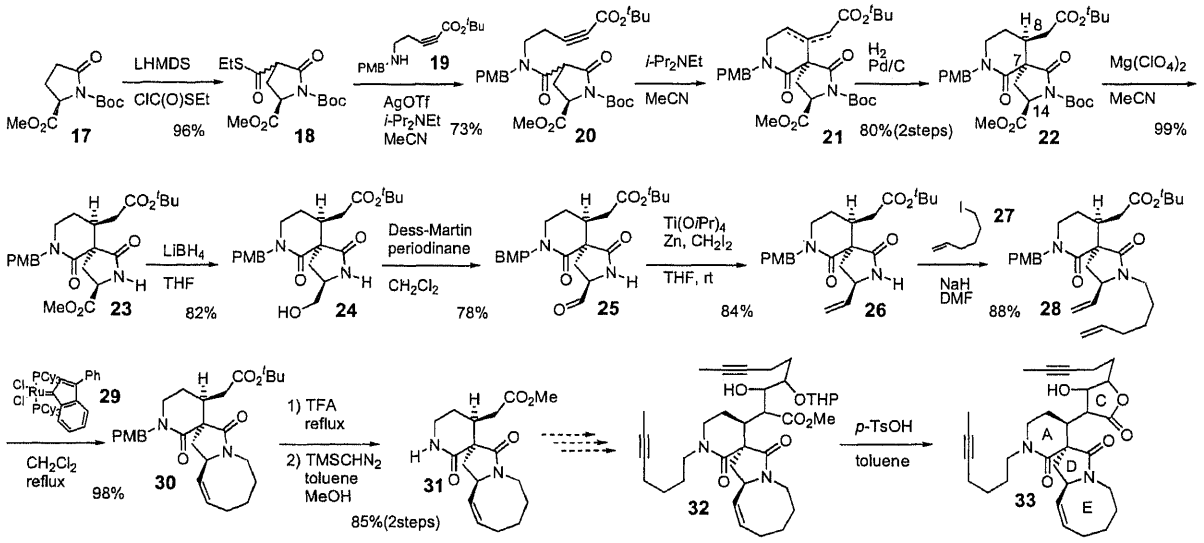
第一に、A. Fürstnerらはring closing metathesis (RCM)を用いたCF環13, E環16のモデル合成を1999年に報告した(Scheme 1)[3a]。アルキン-メタセシスに続くLindlar還元にてシスオレフィンを選択的に構築する点が特徴である。

Scheme 1. A. Fürstnerらの合成法*J. Am. Chem. Soc.* *121*, 11108-11113 (1999).

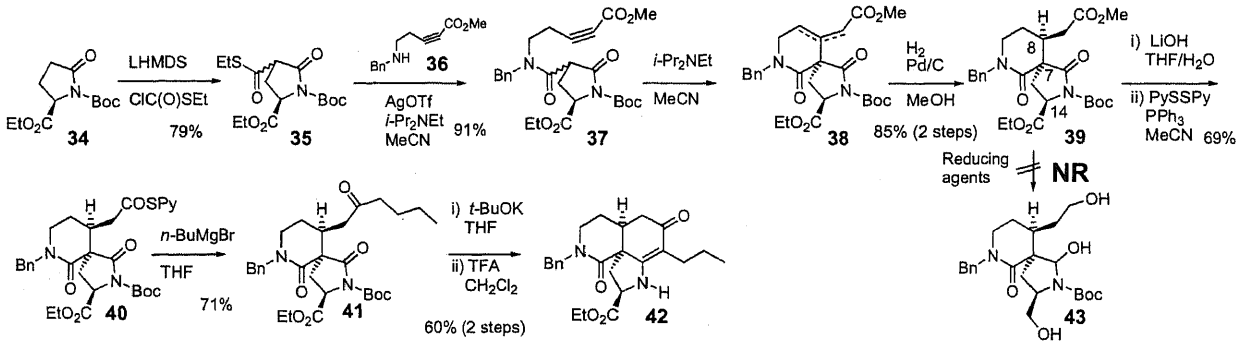


第二に、同じくA. Fürstnerらは、RCMを用いたACDE環33の合成を2001年に報告した(Scheme 2)[3b, 3c, 3d]。中心骨格22の構築には、K. M. J. Brandsら(Merck社)の製法(Scheme 3)[4]を直接採用し、鍵となる3つの不斉点(7, 8, 14位)を構築した。全合成に向け、A環, D環のラクタムの選択的還元とB環の構築が大きな問題である。

Scheme 2. A. Fürstnerらの合成法*Chem. Eur. J. 7*, 4811-4820 (2001).

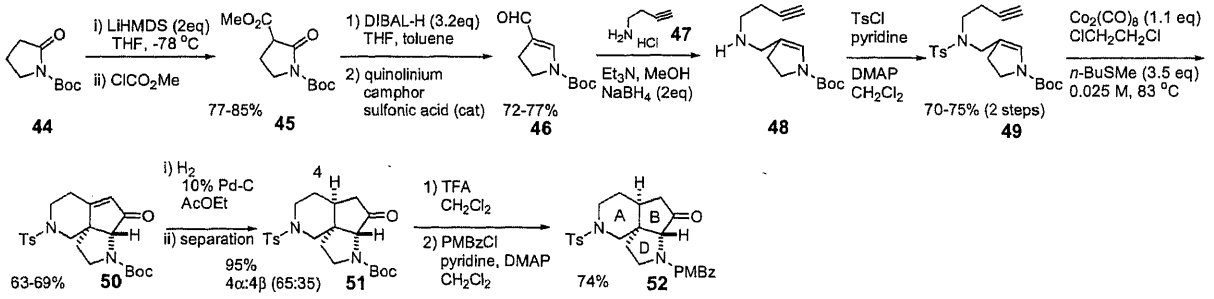


Scheme 3. K.M.J. Brandsらの合成ルート *Tetrahedron Lett. 39*, 1677-1680 (1998)



第三にP. MagnusらのABD環52の合成がある[3e] (Scheme 4)。Pauson-Khand反応を利用したアプローチとしては興味深いが既に立体障害の影響があり、全合成への適用は難しい。

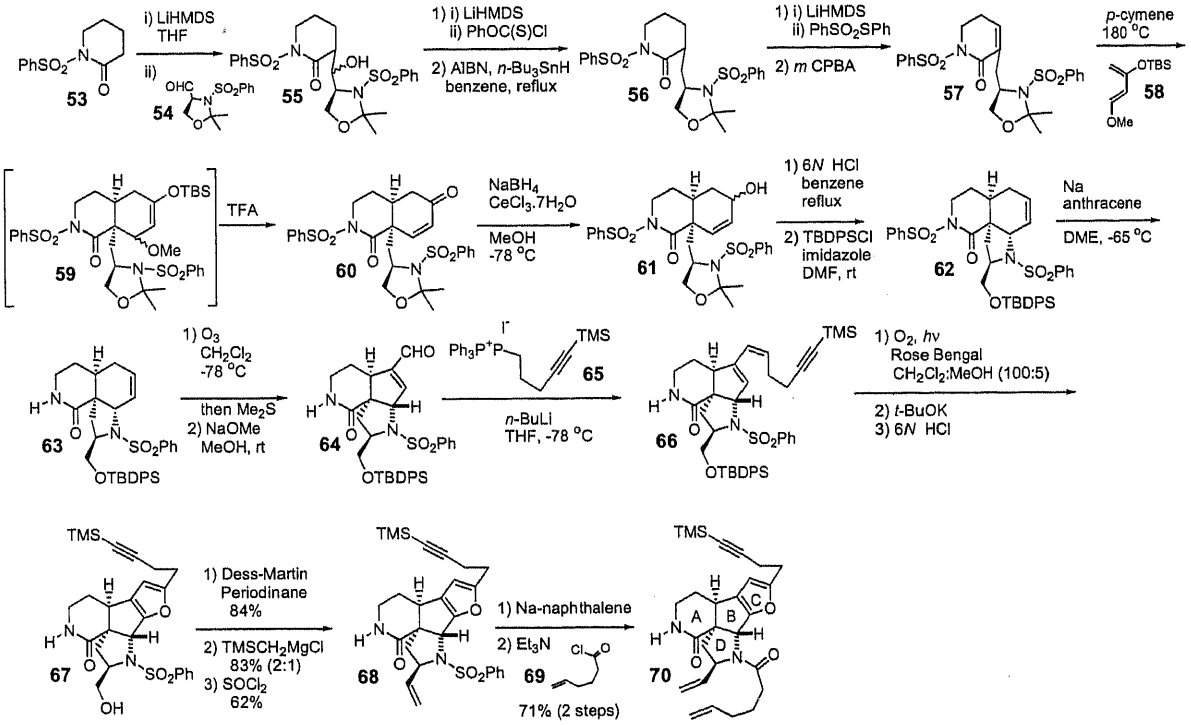
Scheme 4. P. Magnusらの合成法*Tetrahedron Lett. 43*, 947-950 (2002).



第四に未投稿であるが、中川・西田・小野らの合成結果がある(Scheme 5)[3f, 3g]。これは、内田ら[5]によって開発された光学活性Diels-Alder環化体60を官能基変換する方法であり、鍵の中心骨格68の合成に成功している。このルートは次に述べるナカドマリンA (1)の

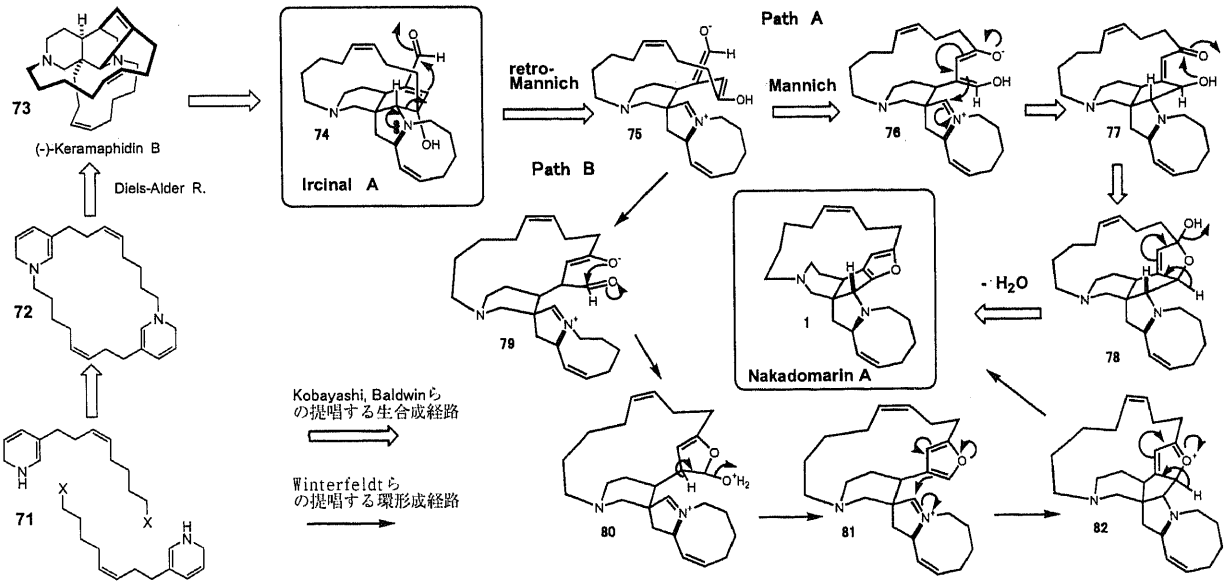
生合成ルートにおいて最後のフラン環の環化を示した点が興味深い(Scheme 6, Path A)。

Scheme 5. 中川・西田・小野の合成法



さて、ナカドマリンA (1)は、生合成プロセス[1] も興味深く、ジヒドロピリジン72の分子内Diels-Alder反応を経由して生合成 [6]されるイルシナールA (74)が、逆マンニッヒ反応につづくマンニッヒ反応によって環化した後、フラン環が形成されたと小林, Baldwinらによって推測された(Scheme 6, Path A)。またフラン環が形成された後、イミニウムカチオン中間体81に対して環化が進行するプロセスをE. Winterfeldt [7]らは提唱した(Scheme 6, Path B)。

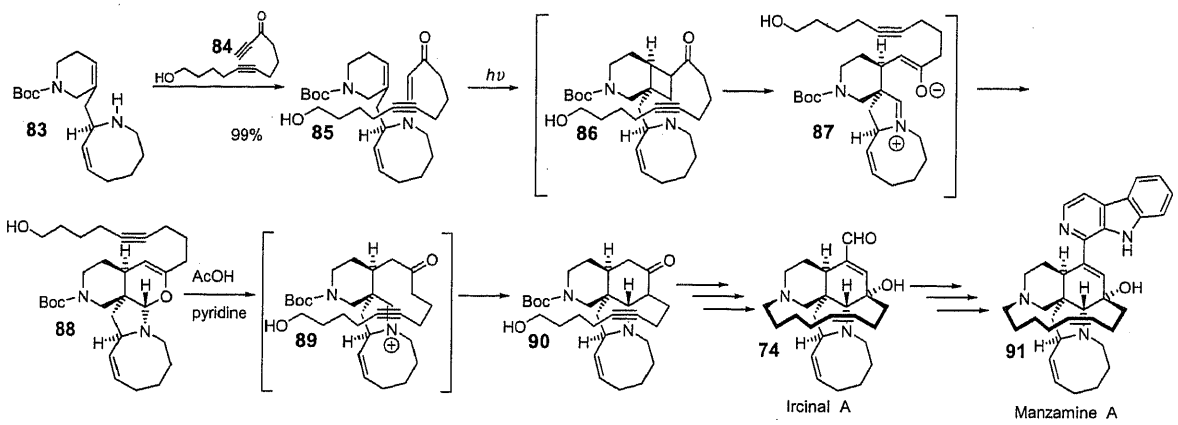
Scheme 6. ナカドマリンAの生合成経路(推定)



この共通のイミニウムカチオン中間体 87(Scheme 7)は、生合成だけでなく化学合成においても重要であり、J.D. Winklerらのマンザミン A (91)の最初の不斉全合成[8](1998年)にも

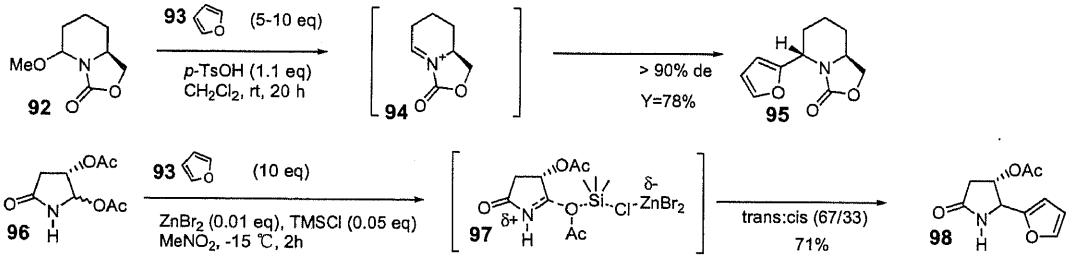
巧みに活用されている。

Scheme 7. J.D. Winklerらによるマンザミンの最初の不斉全合成



そこでイミニウムカチオン中間体81(Scheme 6)に相当するスピロ構造を経る合成戦略が理想と考えた。実際、ナカドマリンA (1)の生合成中間体(推定)94のような化学合成も、分子間反応であるもののC. Lhommet, 野添らの例[9]がある(Scheme 8)。しかし、フランは官能基として弱いためフランを5当量以上、場合によっては反応溶媒として使用している。

Scheme 8. 分子間カチオン環化の反応例

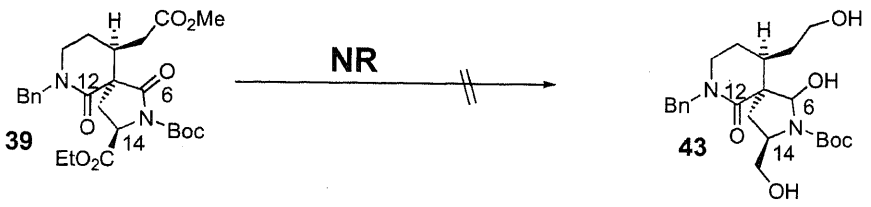


よって、このフランの不安定さのためか、意外にも基質の合成に多段階を要する分子内反応への適用例はない。そこでフランを有したイミニウムカチオン前駆体の合成と、イミニウムカチオンの発生方法がナカドマリンA (1)の中心骨格構築法の鍵と考えた。

イミニウムカチオン前駆体には、他のマンザミン類の合成に適用可能なようにスピロ-γ-ラクタム構造が考えられた。その視点でマンザミンアルカロイドの数多い合成戦略を調査した結果、MerckのK.M.J. Brandsら[4] (後にA. Fürstnerらは保護基のみを変えて報告)のスピロ-γ-ラクタムを経るエレガントな戦略が有利と考えた(Scheme 3)。

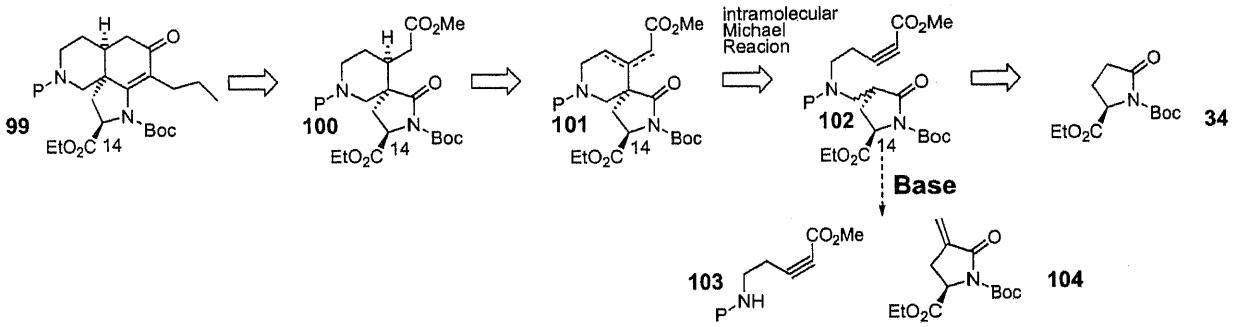
しかし、ナカドマリンA (1)の全合成を達成する上で、K.M.J. Brandsらも述べている問題点(Scheme 9)を解決する必要があった。即ち、立体障害と官能基の影響のために金属ハイドライドでの還元等では6位のアルデヒド等価体への還元が上手くいかなかった点である。

Scheme 9. Brandsらの合成ルートの問題点



39の6位が求核種を受けにくい現象は、当研究室でのマンザミン類の合成研究からも予想されるようにA環ラクタム(12位カルボニル基)の立体障害に起因すると考えた。というのは同様にA環ラクタム(12位)のアミン基への還元も困難であり、全合成を達成するには12位をメチレンにする必要があると考えた。そこで問題の12位がメチレンの誘導体として次の合成ルート(Scheme 10)を考えたが、K.M.J. Brandsらの戦略を適用しただけでは塩基性条件での分子内マイケル(102→101)が進行するのではなく、側鎖自体が逆マイケル反応(102→103, 104)を受け、適用不可と判断した(後の検討で確認済)。また、還元等の塩基による14位側鎖のエピ化の問題もケアする必要がある煩雑さがある。

Scheme 10.　スピロ-γ-ラクタムへの逆合成解析



そこで筆者らはこれらの問題を克服したスピロ-γ-ラクタム誘導体の合成法を考案[10]し、(*S*)-(+)-ナカドマリンAの最初の不斉全合成を達成した。そして(-)-ナカドマリンA(天然由来)の絶対配置を(*R*)と決定した。本論文は、以下の四つの章より構成される。

第一章　ナカドマリンAの逆合成と検討方針
第二章　スピロ-γ-ラクタムによる四環性中心骨格の構築および五環性化合物のモデル合成
第三章　ナカドマリンA (ラセミ体)の全合成
第四章　光学活性ナカドマリンAの不斉全合成, である。以下、順に述べる。

本論

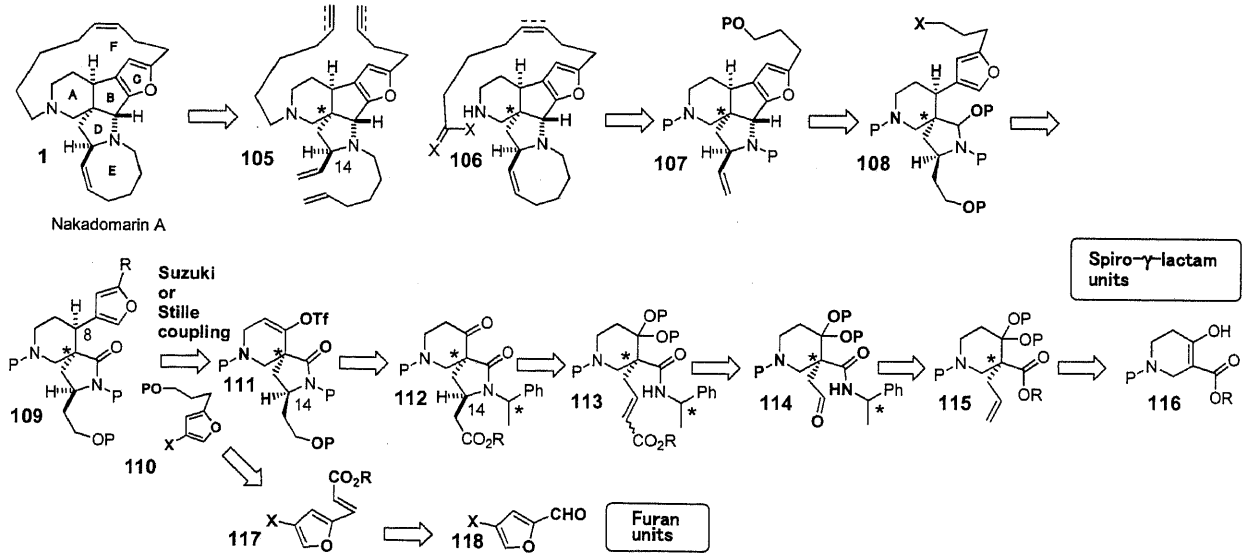
第一章 ナカドマリンAの逆合成解析と検討方針

第一節 ナカドマリンAの逆合成解析

ナカドマリンAは、フラン環を含む8/5/5/5/15/6と高度に縮合した縮環構造を有する。中でも母核のABCD環部は、立体障害に起因する官能基変換や立体選択的な構築が困難と予想した。そのためABCD環部には、不要な官能基(特に12位はメチレンである必要がある)を付さずに合成する点が重要と判断した。またABCD環部を構築後、ABCD環部より遠いもしくは外側のテザー部(E環, F環)を順次構築する方針とした(Scheme 11)[12]。 要点を以下に示す。

1. テザー部(E環部, F環部)の立体選択的な構築と官能基や保護基による区別
2. 母核(ABCD環部)の二つのアミノ基の官能基や保護基による区別
3. 7位不斉炭素を含む母核(ABCD環部)の立体の制御

Scheme 11. ナカドマリン Aの逆合成解析



第一に、テザー部の構築には、RCM[11]または高次希釈条件でのラクタム化(アミノ化)[8a, 12]の適用を計画した。またテザー部は、生合成的に等価であり、適切な時期での官能基変換が可能なように保護基による区別が必要である。

第二に、テザー部の構築に連動して、二つのアミノ基を活性化する必要がある。

第三に、Winterfeldt-小林らの提唱する生合成ルートを応用し、イミニウムカチオン中間体を経たフランの分子内環化反応を計画し、スピロ-γ-ラクタム109を得た。109は、クロス

カップリングに次ぐジアステレオ選択的な還元にてフラン側鎖**110**とスピロ-γ-ラクタム**111**に解析した。**111**の14位には、分子内マイケル環化反応[13]による熱力学的もしくは速度論的な構築を計画した。これらが制御できなくとも光学活性フェニルエチルアミンをキラル補助基とした分子内マイケル環化反応[14]にて構築可能と考えた。このキラル補助基であるフェニルエチルアミドは3位(四級炭素)の光学分割剤(ジアステレオマーアミド法)として機能し検討初期に不斉源を得る手段のひとつになると考えた。また不斉化には不斉アリル化[15]の適用も可能と考えた。その結果、アクリル酸メチルとベンジルアミンから3工程で合成される4-オキソピペリジンカルボキシレート**116**が逆合成された。この合成法は、8位, 14位の各種ジアステレオマーの合成, フラン誘導体の合成, 他のマンザミンアルカロイドの合成が可能な合成ルートになると期待した。

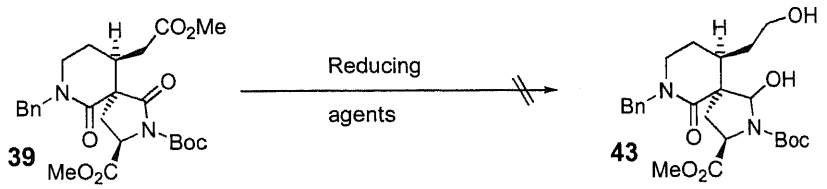
以上の合成戦略を、次の三つの方針に従い検討を開始した。

1. U.K. Panditら[6b]のように14位が無置換のモデルにて反応性や物性等の問題点を把握する。
2. 初期の原料(スピロ-γ-ラクタム)はカラムクロマト精製を殆ど要さない数百グラムスケールで簡便に合成できる方法を目指す。
3. キラルHPLCによる光学純度[16]の判定のためにラセミ体, 光学活性体の順に合成する。

第二節 ナカドマリンAの逆合成解析の問題点の検証

K.M.J. Brandsらは、立体障害と官能基の影響のために金属ハイドライドでの**39**の還元は上手くいかなかったと報告した[4]。

Scheme 12　Brandsらの合成ルートの問題点



そのため、スピロ-γ-ラクタムのルートを実施するにあたり、Brandsのルートと同様、我々のルートでも立体障害と官能基に起因する二つの問題を事前に確認する必要があった。

1. イミドカルボニル基(6位)のアルデヒド等価体への選択的還元の問題,
2. 8位ケタールの脱保護の問題, である。

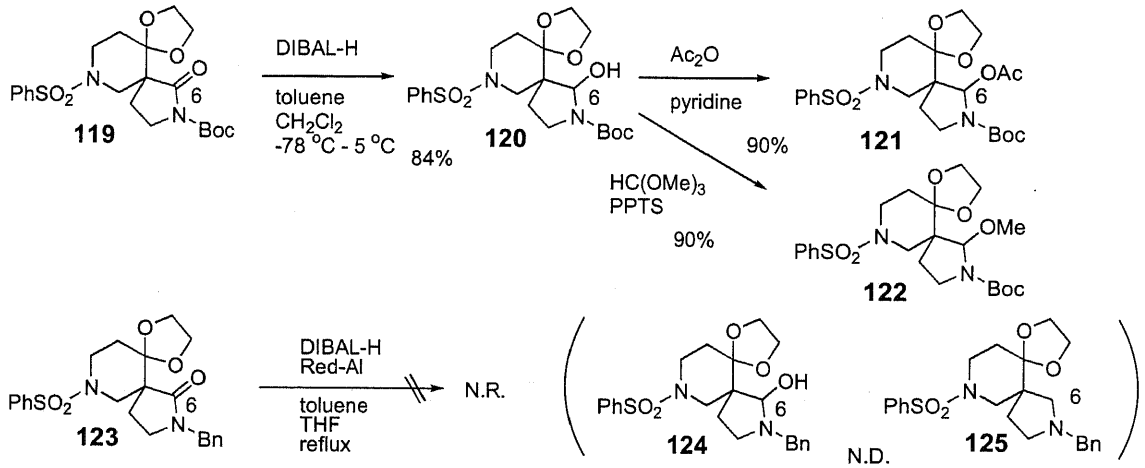
そこで、6-8位の立体障害の問題がより大きいアセタール体にて2項目をモデル実験した。

第1のモデル実験に、K. M. J. Brands (Merck社Process部門)の反応系で問題となったイ

ミドの1,2還元を試した。この1,2還元が進行しない理由は、A環ラクタムのカルボニル基がD環イミドの6位を極性基にて電子的に塞いでいるか、A環ラクタムのカルボニル基のキレーションに基づく還元剤の接近の妨害によりD環イミドの6位の還元を妨げている，と考察した。そこで原因と推察されたA環のラクタムのカルボニル基がないモデル**119**を水素化ジイソブチルアルミニウム(DIBAL-H)にて1,2還元すると目的のアミナール**120**が得られた。このアミナール体は、不安定なため、オルト蟻酸エステルにてエーテル化もしくは無水酢酸・ピリジンにてアセチル化した。

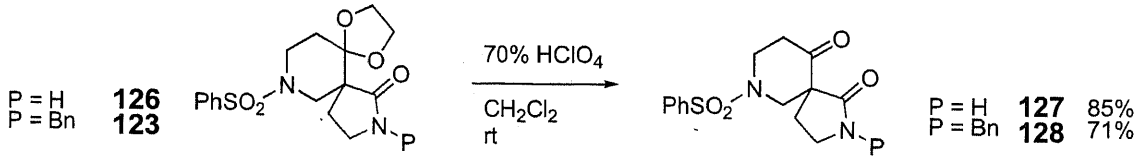
一般にアミナール化において還元基質として電子吸引性基の付加したBocイミドやアリールスルホニルイミド[17]を用いる必要がある。これは、中間体のキレート効果により過剰な還元剤によるアミンへの過還元が進行しにくい点が利点である。それに対して電子供与性基で保護されたベンジルラクタム等を用いると選択的な還元が困難である。即ち、アミナールでは殆ど停止できずに過還元が進行し、アミン体を主生成物として与える(Scheme 2, Fürstnerらの問題点)。

Scheme 13　イミドカルボニル基(6位)のアルデヒド等価体への選択的還元のモデル実験



第2のモデル実験に、8位ケタール**126,123**の脱保護を検討した。8位ケタールは、スピロ-D環の立体障害のため濃塩酸やCSA等の強酸触媒による通常の脱ケタール化の条件[18]では脱保護されなかった。しかし、70%過塩素酸[19]にて酸化的に酸開裂すると脱ケタール化されると判明した。

Scheme 14　脱ケタール化のモデル実験



以上のモデル実験は、立体障害が大きく反応性の低い6位, 8位を選択的に官能基変換できることを証明した重要な実験となった。

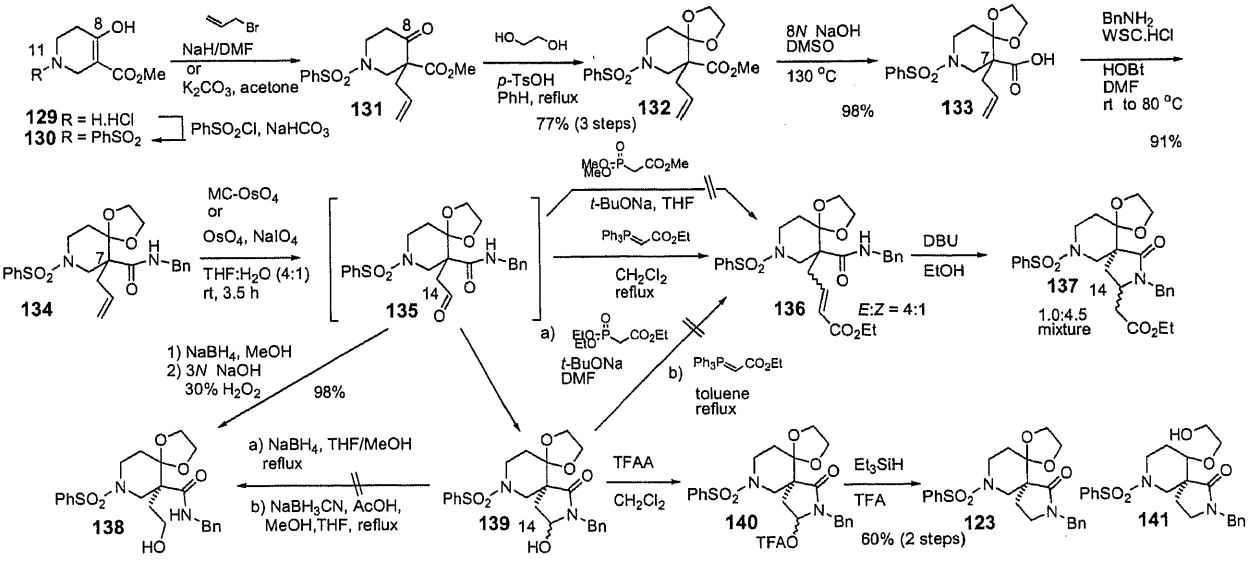
第二章 スピロ-γ-ラクタムによる四環性中心骨格の構築および五環性化合物のモデル合成

第一節　14位無置換 スピロ-γ-ラクタムのモデル合成

先行実験を目的に14位が無置換のスピロ-γ-ラクタムを合成した(Scheme 15)。

出発原料に、ベンジルアミンとアクリル酸メチルから3工程にて合成されるメチル 4-オキソピペリジンカルボキシレート**129**[20]を選択した。通常のカルボアミド型保護基[21]を用いた際に問題となるアミドロートマーの解消と結晶性の向上を目的に11位をベンゼンスルホニル基で保護[22]し、**130**を得た。次に不斉反応の適用も視野に入れたアリル化反応[15, 23]にて**131**を得た。**131**の8位ケト基の互変異性の抑制と結晶性の向上を目的に環状ケタール[18]で保護し、ケタール体**132**を結晶として収率77%(3工程)にて得た。**132**のエステルをアルコール中での塩基性加水分解に付すと、基質が難溶のために加水分解が全く進行しなかった。そこでDMSOを溶剤とし、高温(130 °C)で加水分解してカルボン酸**133**を得た。このカルボン酸**133**をWSC・HCl/HOBtにてベンジルアミンと縮合し**134**を得た。このカルボン酸**133**は、反応性が低く、酸塩化物法以外の単純な縮合条件では、HOBtの添加だけでなく加熱による活性エステルのアミドへの変換が必要だった。次いでアミド**134**のアリル基を四酸化オスミウム(OsO_4)/過ヨウ素酸ナトリウム($NaIO_4$)にて一工程で酸化開裂[24]するとアルデヒド体**135**が自発的に分子内閉環したアミナール[25]**139**が得られた。これをトリフルオロ酢酸中、シラン還元[26]するとアミナールが還元され目的の14位が無置換のスピロ-γ-ラクタム**123**が得られた。しかし、トリフルオロ酢酸中でのシラン還元は、決して原料合成に適した方法でなく、ケタール基の還元開裂体を副生した。

Scheme 15　スピロ-γ-ラクタムのモデル合成



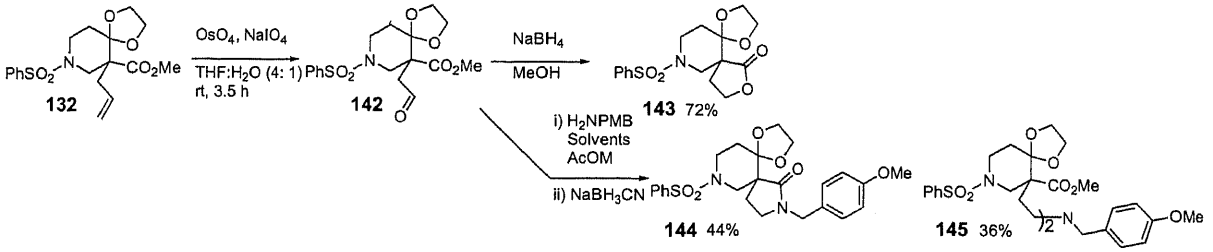
原料合成の際に、中間体のアルデヒド体**135**が抽出液の減圧濃縮中に析出し、ろ取によって単離できた(収率30%)。このアルデヒド体**135**をWittig反応[25]にてαβ不飽和エステル**136**に変換し、分子内マイケル環化にて14位側鎖の導入の可能性が見出せた。しかし、スピロ-

γ-ラクタム**137**の原料合成法としては効率が悪く、またこの時点では四環性中心骨格(ABCD環)の構築の問題を優先する必要があったため一時中断した。

Scheme 15のルートが煩雑だった原因は、$OsO_4/NaIO_4$酸化開裂にて生成したアルデヒド**135**のアミド-NHとアルデヒドが自発的に分子内閉環してアミナール**139**を生成する点にある。そこでNHのプロトンを有さないエステル体**132**を$OsO_4/NaIO_4$酸化開裂に付して得られたアルデヒド**142**を還元アミノ化-分子内ラクタム化反応[27]にて構築することにした。

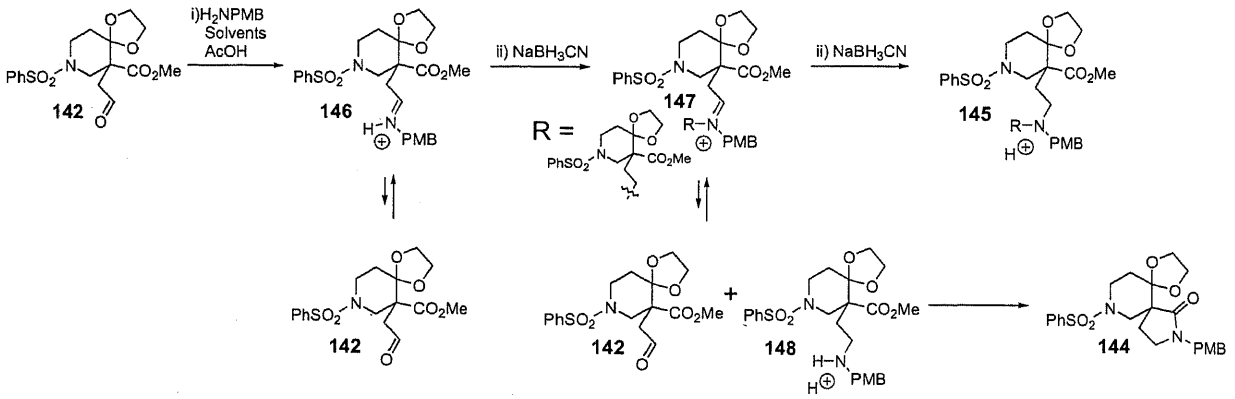
更に、後の検討でベンジルラクタムは接触還元にて脱保護できなかったのでこの時点で保護基を*p*-メトキシベンジル(PMB)に変更することにした[28]。

Scheme 16　還元アミノ化-分子内ラクタム化反応



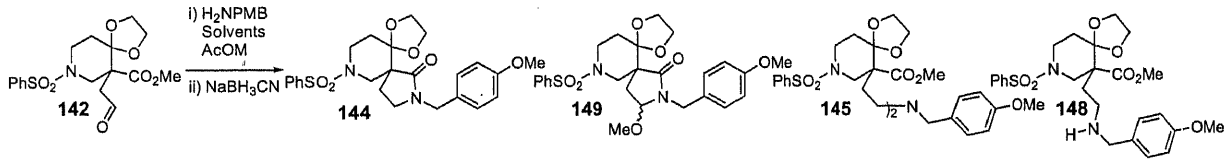
しかし、意に反して生成したものは分子内ラクタム**144**だけでなく二量体**145**もあった(Scheme 16)。この二量体**145**は、還元条件が酸性のために、ラクタム化前の2級アミンが酸触媒の平衡にて生成するアルデヒドと過剰に還元アミノ化され、副生する。文献検索の結果でも1級アミンの2級アミンへの還元アミノ化は、極性基(NH, OH)でShiff塩基の非共有電子対をマスクしている例以外は少なく、アミンを過剰に用いる方向でしか収率の向上は望めなかった。

Scheme 17　還元アミノ化-分子内ラクタム化反応の機構



そこで還元アミノ化-分子内ラクタム化反応を検討した(Table 1)。その結果、酢酸を1.0当量用い、過剰の*p*-メトキシベンジルアミンとともに水素化シアノホウ酸ナトリウム還元して1時間ほどで生成する2級アミン**148**を長時間加熱して分子内ラクタム化すると収率77%にて**144**が得られるようになった。

Table 1　還元アミノ化-分子内ラクタム化反応の検討

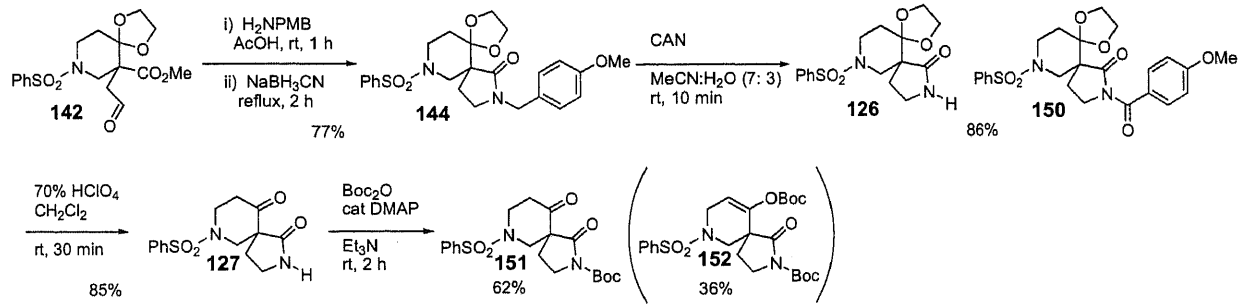


No	溶媒(倍量)	Additive(eq)	H_2NPMB	HPLC (area%) 144 (%)	149 (%)	145 (%)		148 (%)
1	MeOH (10)	AcONa (1.0)	1.1 eq	27.6	0.9	12.1	(16.9)	9.2
2	MeOH (10)	AcONa (1.0)	3.3 eq	42.3	1.7	2.9	(4.1)	14.9
3	MeOH (10)	AcONa (1.0)	5.5 eq	36.8	1.6	1.0	(1.4)	6.2
4	THF (10)	AcONa (1.0)	1.1 eq	10.3	5.7	---	---	17.1
5	THF (10)	AcONa (1.0)	3.3 eq	6.5	14.3	---	---	14.7
6	MeOH (10)	AcOH (1.0)	1.1 eq	30.6	---	22.5	(31.5)	---
7	MeOH (10)	AcOH (0.5)	3.3 eq	31.6	---	3.7	(5.2)	6.4
8	MeOH (10)	AcOH (1.0)	3.3 eq	73.0	---	5.3	(7.4)	---
9	MeOH (10)	AcOH (3.3)	3.3 eq	51.4	---	11.0	(15.4)	---
10	MeOH (10)	AcOH (5.5)	3.3 eq	69.4	---	12.6	(17.6)	---
11	MeOH (10)	AcOH (0.5)	5.5 eq	38.6	0.8	---	---	7.8
12	MeOH (10)	AcOH (1.0)	5.5 eq	50.6	---	2.1	(2.9)	6.4
13	MeOH (10)	AcOH (3.3)	5.5 eq	45.2	---	2.2	(3.1)	0.7
14	MeOH (10)	AcOH (5.5)	5.5 eq	49.7	---	7.2	(10.1)	---
15	THF (10)	AcOH (1.0)	1.1 eq	51.6	43.7	---	---	0.9

<HPLC条件> Inertsil ODS-2　φ 4.6 X 150 mm, 0.05 M KH_2PO_4:MeCN (45:55), 1.0 ml/min, 254 nm

次いでCAN酸化[29]にてPMBを酸化的除去した**126**を得たが、イミド体**150**も10%程度副生した(Scheme 18)。しかし、イミド**150**も次工程の脱ケタール化にて除去されるためそのまま次の反応に付した。次にケタール**126**は、スピロ-D環の立体障害のため反応性が低下しており、濃塩酸やCSA等の強酸触媒による脱保護の条件では除去できなかったため、70%過塩素酸[19]でケタールを酸化的に脱保護し目的のケト体**127**とした。この過塩素酸による脱ケタール化では反応が途中で停止するため抽出後再度過塩素酸処理する必要があった。その際、ラクタムのNHが存在すると酸化性成分のスカベンジャーになるためか反応が途中で停滞する傾向を確認した。D環ラクタム*N*の保護基がベンジルの場合2回の処理で反応が完結したが、D環ラクタム*N*がフリーだと5~6回過塩素酸処理する必要があった。よって単純にケタールを除去するだけならベンジル保護体の方が優れていた。

Scheme 18　スピロ-γ-ラクタムのモデル合成



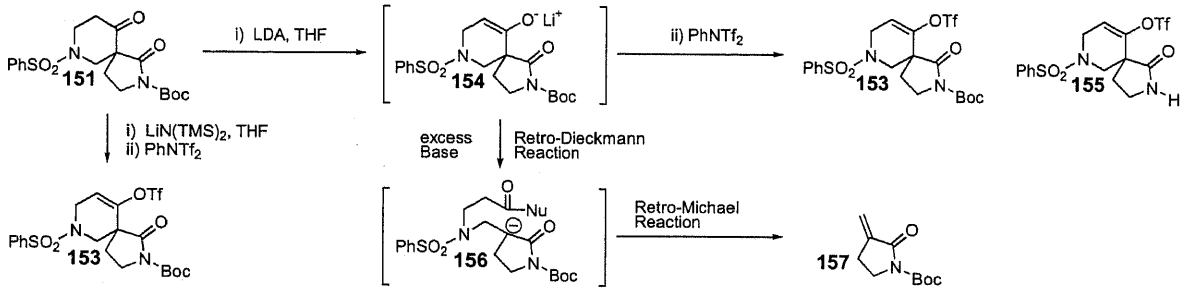
次に**127**のD環ラクタム*N*のBoc化[30]を検討した。検討の初期には基質**127**がTHF(7倍量)に完全に溶解したため、エノールプロトン(エノールBoc体**152**を副生)とD環ラクタムプロト

ンの選択的なBoc化が可能であった。しかし、スケールアップすると127が難溶性の結晶（40倍量以上のTHF溶媒にも溶解しない)となり、溶解度の問題から選択的なBoc化が困難になった。しかし、目的のケト体151を主成績体として合成できたため、副生物のBocイミド152をカラムクロマト精製にて分離して、先に進むことにした。

第二節　14位無置換 四環性中心骨格のモデル合成

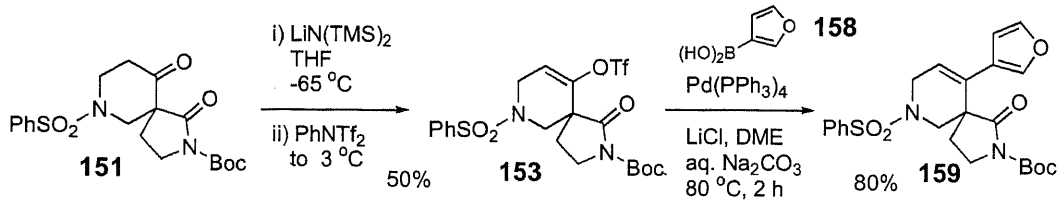
まず鈴木-宮浦カップリングのためのトリフラート153を合成した(Scheme 19)。常法に従い、ドライアイスアセトン冷却下、強塩基とN-フェニルビス(トリフルオロメタンスルホンイミド)を用い、151をトリフラート化した[31]。強塩基としてリチウム ジイソプロピルアミド(LDA)を使うと、後処理の際に副生するジイソプロピルアミンがBocイミド153からの脱Boc化を促進し、155を副生した。そこでより求核性の弱いリチウム トリメチルシリルアミドにてリチオ化した。その際、シリルアミドが1.0当量を超過すると逆Dieckmannに次ぐ逆マイケル反応によってピペリジノン環(A環)が開裂してエキソメチレン体157を副生した。そのため塩基量は、1.0当量を超過しないよう注意を要した。

Scheme 19　トリフラート化と逆Dieckmann反応-逆マイケル反応



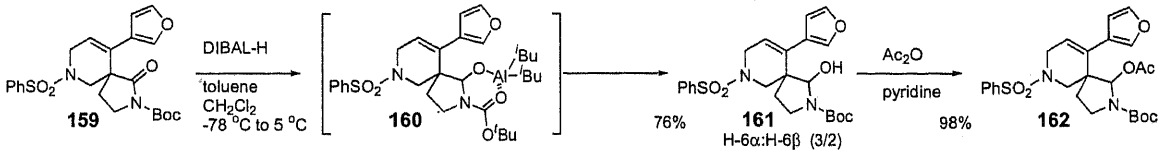
次のボロン酸エステル158とトリフラート153の鈴木-宮浦カップリング[32] (Scheme 20)は、速やかに進行した。しかし、カップリング成績体159はフラン骨格と二重結合が隣接しており、空気酸化にて黄色タール状物へ分解し易く、取り扱いに注意を要した。

Scheme 20　トリフラート化と鈴木-宮浦カップリング



鈴木-宮浦カップリング成績体159のBocイミドを過剰の水素化ジイソブチルアルミニウム(DIBAL-H)にて1,2還元[17]し、アルデヒド等価体であるアミナール161へ変換した(Scheme 21)。この際、中間体のキレート効果により過剰な還元剤によるアミンへの過還元は進行しにくかった。

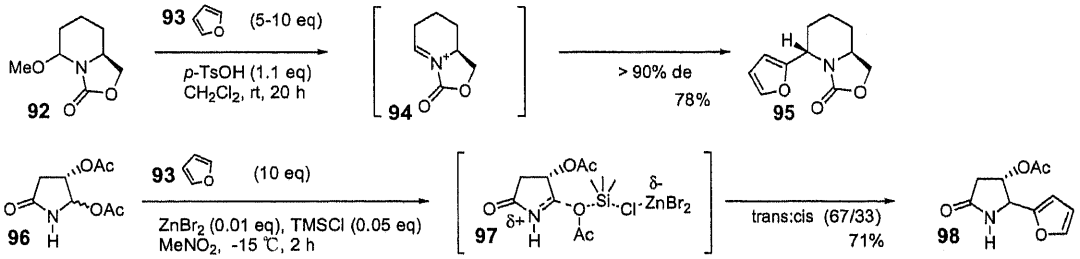
Scheme 21　イミドの還元



次にアミナール**161**を無水酢酸・ピリジンでアセチル化し、**162**を得た。オルト蟻酸メチルやオルト蟻酸エチル[33]にてアミノアセタールにも変換可能であるが、次工程の環化にて脱離性の強い方が好ましいためアセチル体**162**を以後使用した。

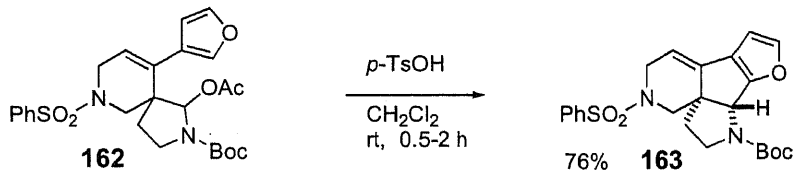
次のイミニウムカチオンへのフラン環の分子内環化反応には、G. Lhommetら, 野添らの分子間反応の条件[9] (Scheme 22)を適用した。

Scheme 22　分子間カチオン環化の反応例



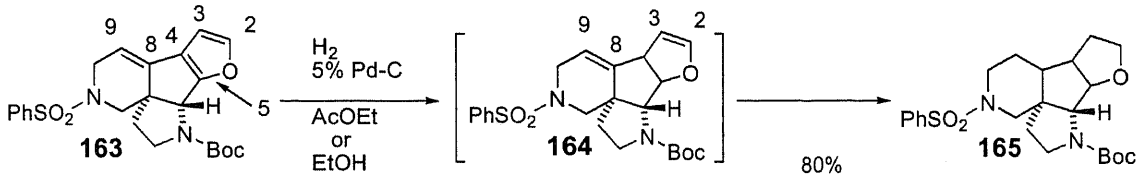
その結果、**162**をCH_2Cl_2中、*p*TsOH.H_2O (1.1 eq)で反応するとアセチル基にて活性化されているために分子内カチオン環化反応(cationic cyclization)が速やかに進行し、目的の四環性化合物**163**を与えた(Scheme 23)。

Scheme 23　四環性中心骨格のモデル合成



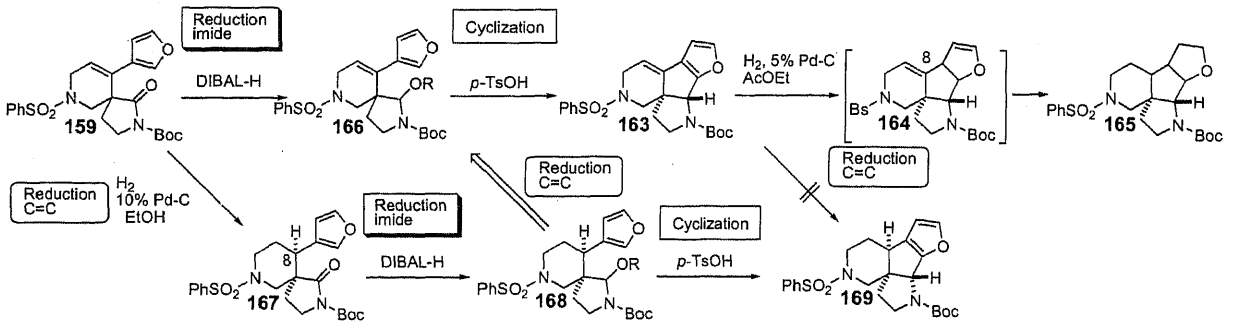
目的の四環性中心骨格が得られたため、8位がαに立体選択的に還元されることを期待し、**163**をパラジウム炭素で接触還元した(Scheme 24)。しかし、還元条件を緩和してもフラン環が優先して還元された[10]。

Scheme 24　四環性中心骨格の還元反応



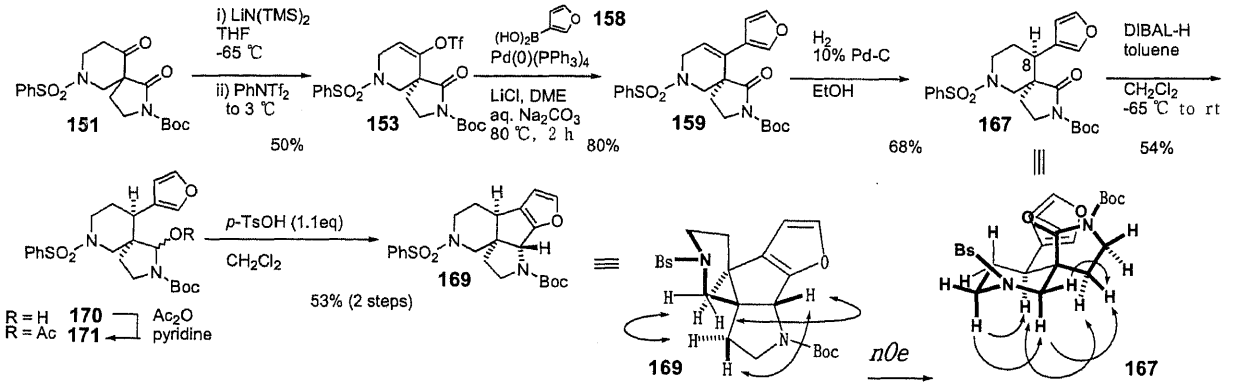
反応を精査したところフラン環4-5位間が先に還元され、次いで残りの二重結合が還元されることが判った。フラン環に大きな歪がかかり、芳香族性が低下したためと考えられる。そこで8位二重結合と共役が寸断されている中間体**159**を先に還元するルートに変更した(Scheme 25)。

Scheme 25　四環性中心骨格の合成経路



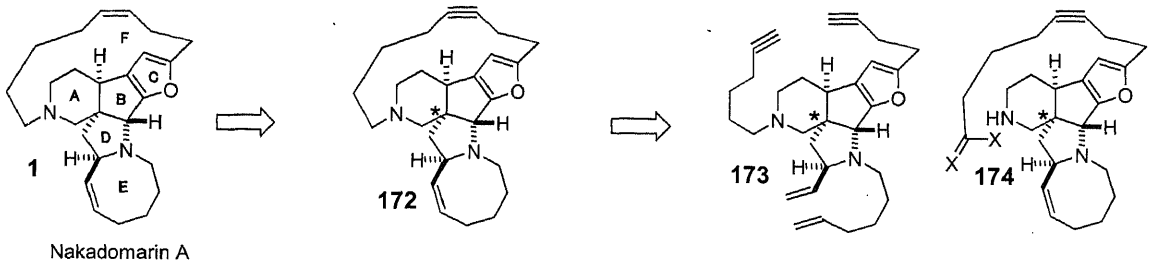
その結果、フラン環をほぼ還元することなし(2%未満)にジアステレオ選択的に8位二重結合の還元が進行し、目的のH-8α体**167**が得られた(Scheme 26)。収率の低下は、生成物の難溶性に起因し、パラジウム炭素に吸着ロスしたためである。この立体化学はnOe実験で決定した(Scheme 26)。得られた還元体**167**を、DIBAL還元に次ぐアセチル化、そして cationic cyclizationによって目的の四環性化合物**169**を得た。

Scheme 26　四環性中心骨格の合成



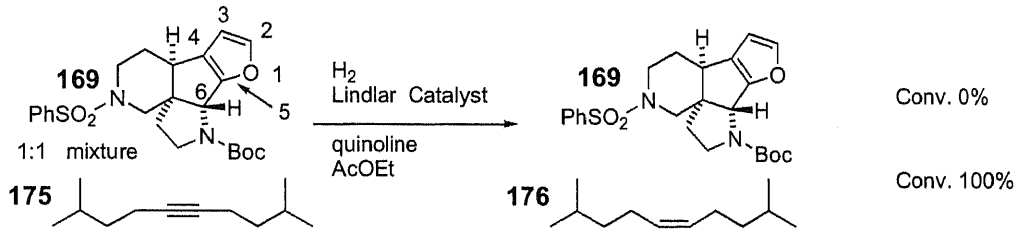
ここまでの検討で四環性の中心骨格**169**の構築法が見出された。しかし、ナカドマリンAの全合成を達成するには、F環の構築のためにアルキンメタセシスの前駆体**173**もしくはJ. D.Winklerらの方法(山口法による分子内ラクタム化法[3a, 8a] に次ぐアルキンのLindlar還元)の前駆体**174**が想定される (Scheme 27)。

Scheme 27　ナカドマリンAの逆合成



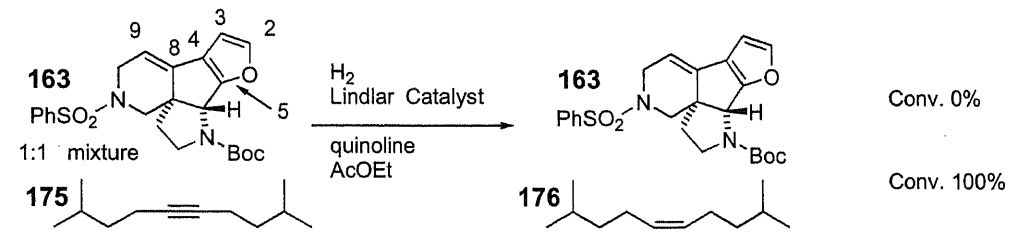
しかし、Scheme 24のように歪がかかったフラン環が還元されやすいならば、B環構築後の還元操作にはフラン環を還元しないよう注意を要する。そこで三重結合の選択的還元の可能性を確認する目的でアルキン化合物**175**と四環性中間体**169**の混合物をLindlar還元[34]し、フラン環の還元反応の選択性を確認した(Scheme 27の仮想中間体**172**はフラン環もアルキンも相当歪がかかっているため反応性が高いと予想された)。実験の結果、アルキン**175**が選択的に還元されcis-オレフィン**176**を与えたがフラン環は全く還元されなかった(Scheme 28)。このため、J.D.Winklerらの方法も適用可能と判断した。

Scheme 28　四環性化合物のLindlar還元実験 1



同様に、四環性化合物**163**をLindlar還元した(Scheme 29)。その結果、アルキン**175**が選択的に還元されcis-オレフィン**176**を与えたが、8位間のオレフィンやフラン環は全く還元されなかった。しかし、Scheme 24の検討のようにH_2, 5%-Pd-C/AcOEtの還元では4-5位間のオレフィンが先に還元されるため、反応性は アルキン>フラン>endo-olefinの順になると判明した。

Scheme 29　四環性化合物のLindlar還元実験 2

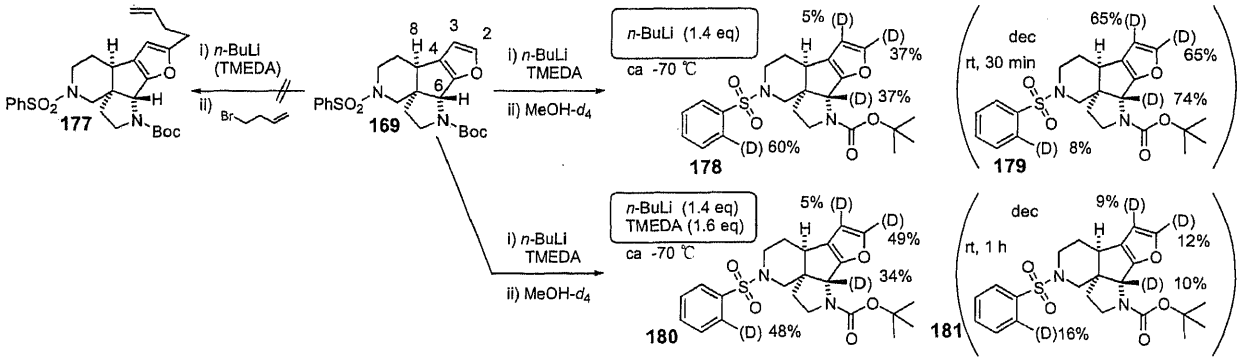


第三節　2位-フラン側鎖の導入の検討

これまでに四環性中心骨格**169**の構築法が見出された。残りは、中心骨格にE環とF環を構築するためのテザー部の導入である。中心骨格**169**ではE環の導入ができないため、F環側鎖の導入から、即ちフラン2位のリチオ化法によるホモアリル基の導入から試みた(Scheme 30)。その結果、求電子剤の1-ブテン-4-ブロマイド(市販品)が導入されなかった(リチオ体結晶の析出を確認済)。そこでリチオ化自体に問題がないことを確認するため、MeOH-d_4によるD化を検討した。その結果、*n*-BuLiまたは*n*-BuLi/TMEDAによるリチオ化法では、D化の位置選択性が低く、目的のフラン2位だけでなく, H-6位, ベンゼンスルホニル基オルト位が同程度リチオ化されていた。この様に、フラン環のリチオ化は効率が悪

いため、予めフランに側鎖を導入して官能基変換する方針とした。

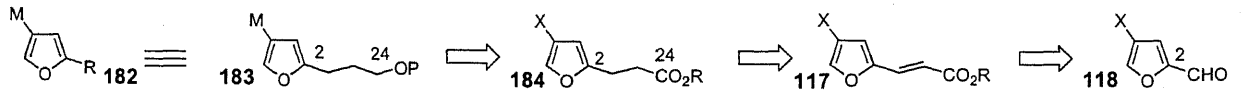
Scheme 30　四環性化合物のリチオ化法によるｱﾙｷﾙ化



第四節 フラン側鎖の合成

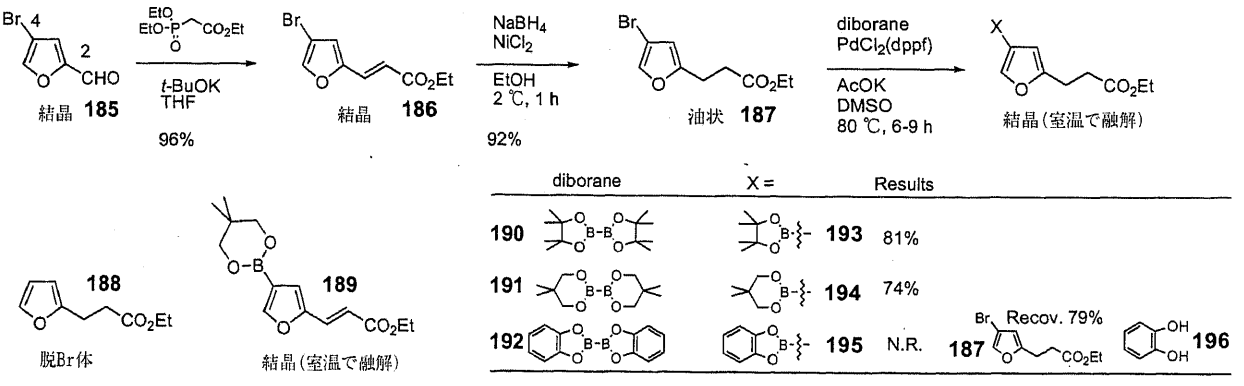
まず序論の逆合成(Scheme 31)に従い、フラン誘導体**182**を逆合成した。フランの4位は、スピロ-γ-ラクタムの8位とのクロスカップリングのために錫またはホウ素等価体の臭素を想定した。またフランの2位は、将来、ナカドマリンAのF環側鎖の足がかりとなるため、24位がオレフィンやアルキン等価体である1級アルコール**183**を想定した。この1級アルコール**183**はHorner-Wadsworth-Emmons反応で得られるαβ不飽和エステル**117**から誘導される。そこで原料には東京化成市販の4-ブロモ-2-フルアルデヒド**185**を選択した。なお、4-ブロモフラン誘導体は空気酸化にて黒色タール状に酸化分解するため、工程の短縮が肝要であった。

Scheme 31　フラン側鎖の逆合成解析



4-ブロモ-2-フルアルデヒド**185**[35]とジエチルホスホノ酢酸エチルとのHorner-Wadsworth-Emmons反応によりC_2伸長し、αβ不飽和エステル**186**を得た(Scheme 32)。

Scheme 32　フラン側鎖の合成

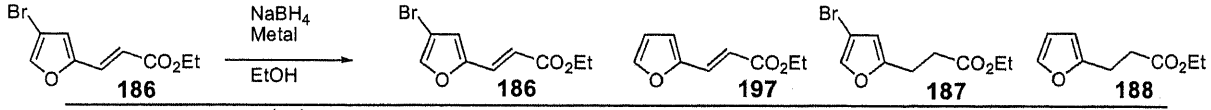


αβ不飽和エステル**186**を佐藤らの1,4還元の条件[36]、即ちメタノール中、塩化ニッケル(II)

触媒を用いテトラヒドロホウ酸ナトリウムにてαβ不飽和エステルを1,4還元した。しかし、メタノール中では還元条件が強く氷冷下5分ほどで1,4還元だけでなく全て脱ブロモ体188に過還元された。そこで還元条件の緩和のため、エタノール溶媒中、0.1当量の塩化ニッケル(II)触媒を用い、テトラヒドロホウ酸ナトリウムで1,4還元(3-4 °C, 1時間)すると、反応の停止とともに低温にて不溶なニッケル触媒をろ去すると4位ブロモを脱離することなく飽和エステル187が得られるようになった。

そこで1,4還元の金属種に銅, ニッケル, コバルトの塩化物, アセテート, 酸化物等を検討した(Table 2)。その結果、ブロモ体/脱ブロモ体 比(Br/脱Br)の高いニッケルが優れていた。他の金属種は2 °Cにて、1,4還元が進行する前に脱ブロモ体188を既に副生した。次に酢酸ニッケルと塩化ニッケルを比較すると、触媒の使用量が多く(触媒のろ別によって反応を停止させるため)、1,4還元の速度が遅い 塩化ニッケルの操作性が優れていた。

Table 2　ブロモフランの1,4還元の検討



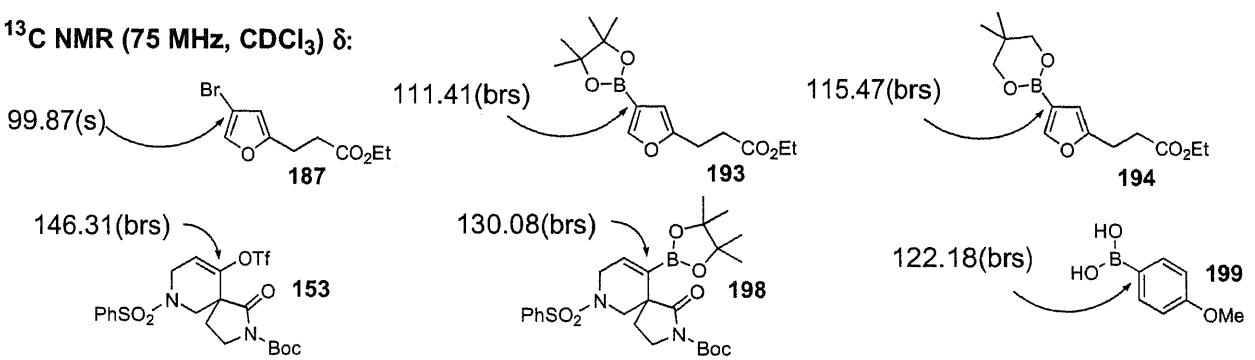
No.	Metal (eq)	temp	time	186	197	187	188	Br/ 脱 Br	変換率
1	Cu^0 (0.1)	2-23 °C	15 h	67	18	13	2	4.00	20
2	Cu^I_2O (0.1)	2-23 °C	15 h	46	19	27	8	2.70	35
3	Cu^IBr (0.1)	2-23 °C	24 h	34	33	35	9	2.23	44
4	$Cu^{II}Cl_2$ (0.1)	2 °C	1 h	56	22	19	3	3.00	22
5	$Cu^{II}Cl_2$ (0.1)	2-23 °C	15 h	0	0	40	60	0.67	100
6	$Cu^{II}SO_4$ (0.1)	2-23 °C	24 h	65	5	28	2	13.29	30
7	$Co^{II}Cl_2$ (0.1)	2-23 °C	3 h	54	16	23	7	3.35	30
8	$Co^{II}Cl_2$ (0.1)	2-23 °C	24 h	3	3	62	31	1.91	94
9	$Ni^{II}Cl_2$ (0.1)	2 °C	1 h	71	-	28	1	99.00	29
10	$Ni^{II}Cl_2$ (0.1)	2-23 °C	15 h	0	0	68	32	2.13	100
11	$Ni^{II}(OAc)_2$ (0.1)	2 °C	1 h	30	0	70	D	> 99.00	70

生成物比は ^1H NMR (300 MHz, $CDCl_3$)の積分比から算出した。

はじめ、リチオ化を経るスズ化を前提にエステル187を還元したが、エステル還元操作によって脱ブロモ体を多量に副生したため、効率が悪く断念した。

そのため2位のエステル側鎖は無変換のまま4位ブロモを変換できる条件として宮浦らの方法[37]によりボロン酸エステル193, 194に変換した(Scheme 32)。ボロン酸エステルの構造は、^{13}C NMRにて4位^{13}Cシグナルの消失を確認し、更にHMBCにて4位^{13}Cと^1Hの相関を確認して決定した(Scheme 33)。

Scheme 33　ボロン酸誘導体のB-C結合の^{13}Cケミカルシフト



後述する次工程の鈴木-宮浦カップリングの際、遊離したボロン酸エステルがトリフラー

トと置換する副反応を改善する目的にてボロン酸エステルの誘導体193, 194を合成した（Scheme 32)。市販のアルコラトジボロン(3種)190-192を比較した結果、ビス(カテコラト)ジボロン192は反応中に加水分解が進行し、クロスカップリングが進行せず、原料を回収した。他の2種[ビス(ピナコラト)ジボロン190とビス(ネオペンチルグリコラト)ジボロン191[38] (WO/98/46265)]では反応が進行した。これらボロン置換フラン193, 194は、不活性ガス下、液状かつ冷蔵では黒色タール状となり1ヶ月程度で分解したが、不活性ガス下、冷凍保存によって結晶化し半年程度の保存が可能になった。

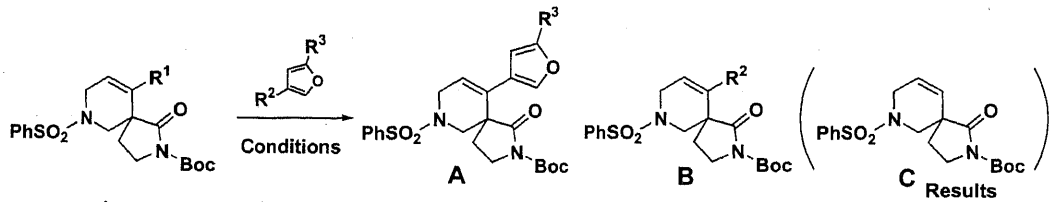
このように4-ブロモフランは液状では黒色タール状に酸化分解するため、結晶化しやすく更なる工程の短縮が可能なαβ不飽和エステル体も同様にボロン酸エステルに変換した誘導体189も合成した。

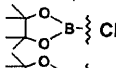
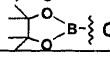
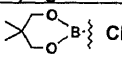
以上よりフランユニットのボロン酸エステル193, 194を2から3工程で安定して供給できるようになった。

第五節 14位無置換 五環性化合物のモデル合成

第三節で合成したトリフラート153と第四節のフランのボロン酸エステル193, 194とを鈴木-宮浦カップリングに付した。その結果、ピナコラトエステル193では従来の変換率80 % (Table 3, No.1)は達成できず、20-30%程度しか得られなかった(Table 3, No. 2,3)。そこでボロン酸エステルを193でなく、ネオペンチルグリコラトエステル194にすると収率が68%に向上した (Table 3, No. 4)。No. 5, 6のようにA環側をボロン酸エステル198にすると、ブロモフランとのクロスカップリングよりも先にD環ケト基の影響でボロン酸エステル198が速やかに加水分解を受け、目的のカップリング体200がほとんど得られなかった。

Table 3　鈴木-宮浦カップリングの検討



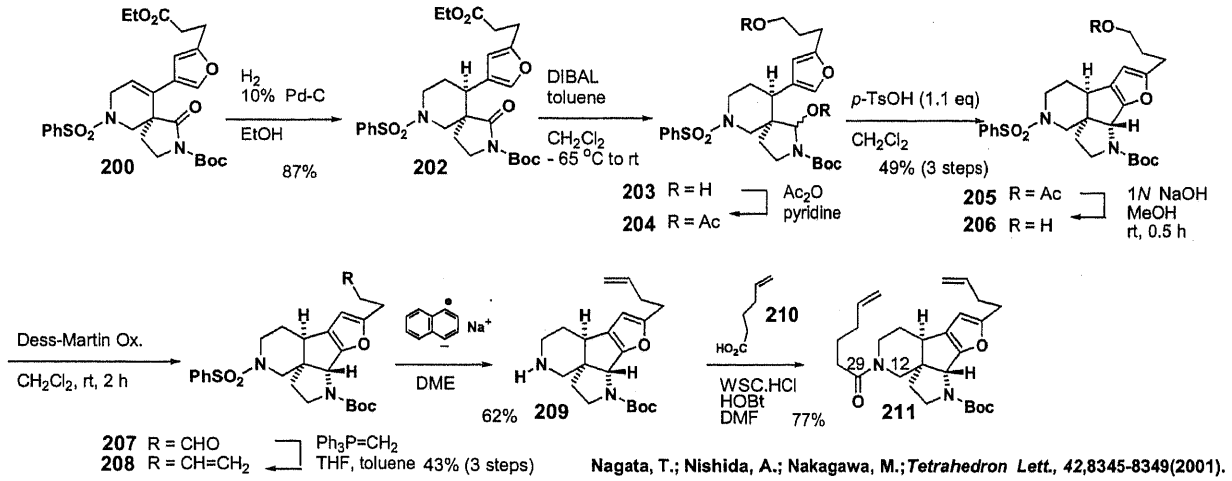
No	R^1		R^2	R^3	Catalysts (5 mol%)	Conditions	Products	Byproducts
1	153 OTf	158	$(HO)_2B$	H	$Pd(PPh_3)_4$	Na_2CO_3, LiCl, DME, 80 °C, 6 h	159 (A) 80%	non
2	153 OTf	193		$CH_2CH_2CO_2Et$	$Pd(PPh_3)_4$	Na_2CO_3, LiCl, DME, 80 °C, 6 h	200 (A) 26%	198 (B) 20%
3	153 OTf	193		$CH_2CH_2CO_2Et$	$Pd(PPh_3)_4$	K_3PO_4, LiCl, DME, 80 °C, 7 h	200 (A) 30%	198 (B) 29%
4	153 OTf	194		$CH_2CH_2CO_2Et$	$Pd(PPh_3)_4$	Na_2CO_3, LiCl, DME, 80 °C, 7 h	200 (A) 68%	non
5	198 	187	Br-	$CH_2CH_2CO_2Et$	$PdCl_2(dppf)$	K_3PO_4, DMSO, 80 °C, 6 h	200 (A) 0.2%	201 (C) 21%
6	198 	187	Br-	$CH_2CH_2CO_2Et$	$Pd(PPh_3)_4$	Na_2CO_3, LiCl, DME, 80 °C, 6 h	200 (A) 6%	198 (B) 57%

以上の検討から、フラン側鎖にはネオペンチルグリコラトボロン酸エステル194、A環側

にはトリフラート153の組み合わせが最も良いと判明した。

次にカップリング体200を立体選択的に接触還元し、202を得た(Scheme 34)。先と同様にイミド202をDIBAL還元した。その際、側鎖のエチルエステルも1級アルコール203に還元した。これらを無水酢酸・ピリジンにて同時にアセチル化し、204を得た。次いでイミニウムカチオン中間体を経る分子内環化反応に付し、2位に側鎖を有する四環性中間体205を得た。アセチルエステル205を塩基性加水分解し、得られた1級アルコール206をDess-Martin酸化[39]にてアルデヒド207とした。次にWittig反応[40]にて末端オレフィン208を得た。208のベンゼンスルホニル基をNa-ナフタレン[41]で還元除去し、2級アミン209を得た。209をWSC・HCl/HOBtにて5-ヘキセン酸210と縮合し、ジエン211に変換した。

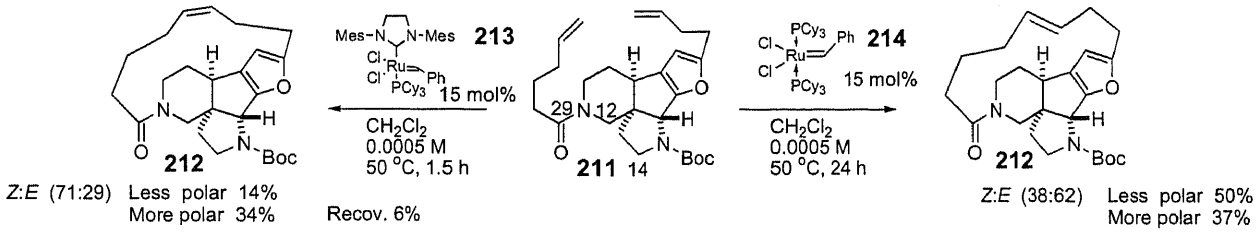
Scheme 34　四環性化合物の変換



Nagata, T.; Nishida, A.; Nakagawa, M.; *Tetrahedron Lett.*, *42*,8345-8349(2001).

ジエン211をRCM(第1世代Grubbs試薬214[42] 15 mol%, 0.0005 M, 50 °C, 24 h)に付し、目的の5環性化合物212(*Z*:*E*比38:62推定)*1 の合成を達成した(Scheme 35)。五環性化合物212の構造は、^{1}H NMRから、ジエン211のA環のアミドロートマーが消失し、代わりに29位カルボニル基が12eq位側に固定された環構造が形成されたことが支持された(12eq位プロトンが29位カルボニル基の異方性効果で極端に低磁場シフトしている)。この異方性効果によりF環がD環に対してトランスの位置関係にあることが判明した。24位オレフィン部の幾何異性は、NOESYにより、アリル位とオレフィンにnOeが観測されたものを*E*体と決定した。しかし、^{1}H NMRの測定溶媒を変えてもピークが完全に分離しなかったためオレフィン部のJ値の決定にまで至らなかった。

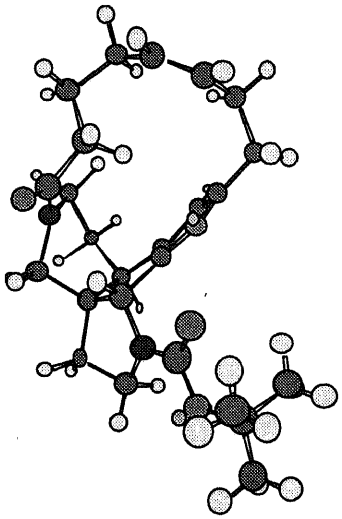
Scheme 35　五環性化合物の合成



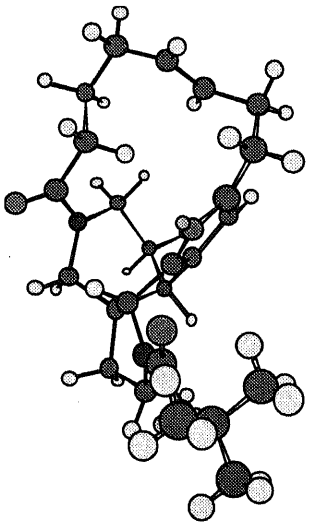
次にビスオレフィンを第2世代Grubbs試薬213[43](15 mol%)を用いてRCMに付した(0.00

05 M, 50 °C, 1.5 h)。その結果、第1世代Grubbs試薬**214**の反応とは逆に、目的の**212** (*Z*体)が過剰に得られた。しかし、目的物以外の構造不明な化合物が副生した(環化体 収率48%)。

Fig. 2　五環性化合物のモデル図



24*Z*



24*E*

以上、目的の五環性モデル**212**が構築できると判明したため、次に14位側鎖を有する系にて合成を検討することにした。

第三章　ナカドマリンA(ラセミ体)の全合成

第一節　14位置換スピロ-γ-ラクタムの合成

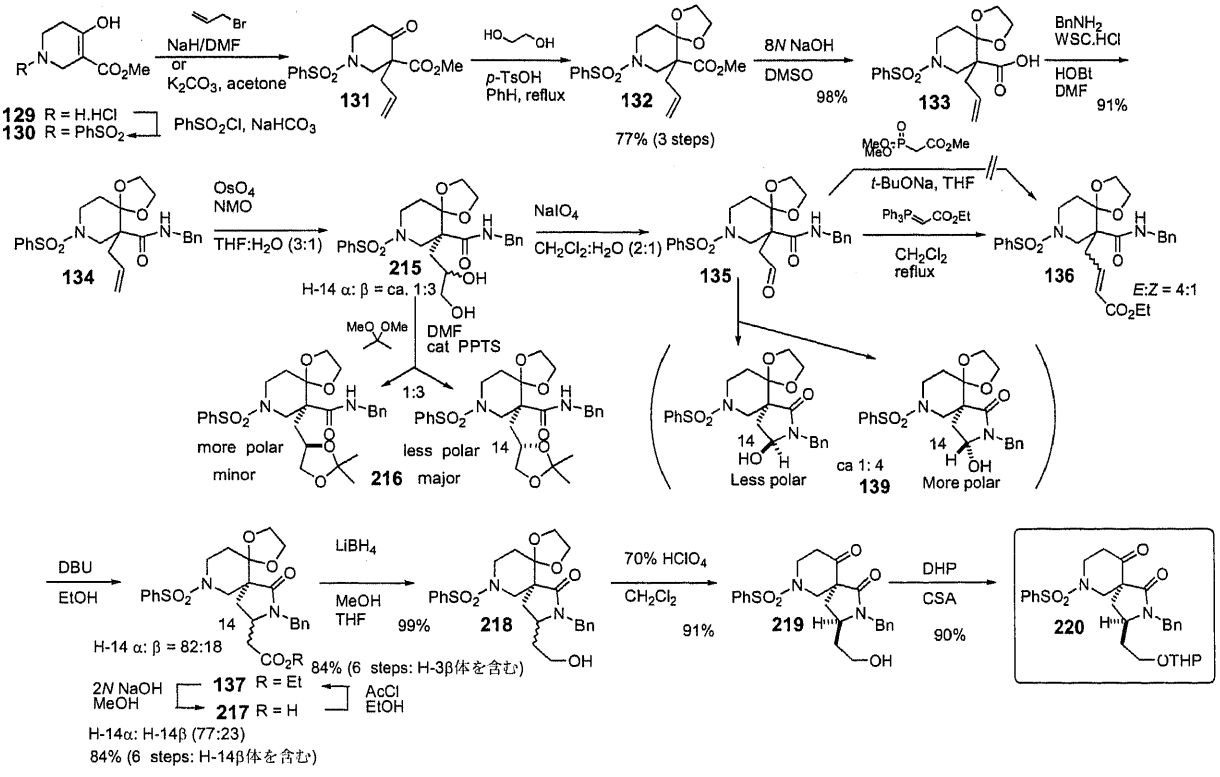
$OsO_4/NaIO_4$酸化開裂(one-pot法)[44]によるアルデヒド**135**の合成は、30gスケールが限界であり、収率も低く(約30%)、合成上大きな問題となっていた(Scheme 15)。その原因は目的のアルデヒド**135**が、Wittig反応に抵抗するアミナール**139**[H-14α:H-14β (約1:4)]に自発的に分子内閉環する点(半減期約3時間), 中間体のジオールや副生する$NaIO_3$が析出して不均一となり、再現性がない点であった。

そこで酸化操作を2段階とした(Scheme 36)。まず、V. VanRheenenらの方法[45] (OsO_4/NMO酸化)にてジオール化**215**を収率90%-96%で得た。反応液から析出したジオール体**215**はろ取にて簡便に単離することができた。ジオール**215**のH-14位の立体化学は、アセトナイド**216**[46]に変換した後、H-14α:H-14β (1:3)と決定した。

ジオール**215**の酸化開裂は、D. Y. Jacksonの方法[47] を改良し、適用した。即ち、$NaIO_4$の水溶液を添加し、ジオール**215**が反応後にCH_2Cl_2に完全に溶解して均一になるように条件を設定し、そのCH_2Cl_2層を直ちに分取する方法とした。CH_2Cl_2抽出液を$MgSO_4$乾燥し、$MgSO_4$のろ去時に次工程のWittig試薬で**135**を捕捉し、不安定なアルデヒド体**135**の存在時間を短縮した。

なお参考に述べるが、以下のアリル基の酸化開裂法は、生産効率の問題から不適当であった。例えばオゾン酸化[48] は、難溶な基質**134**が低温のTHF中でも析出し未反応であった。また三塩化ルテニウム/過ヨウ素酸 酸化開裂[49] も未反応であった。

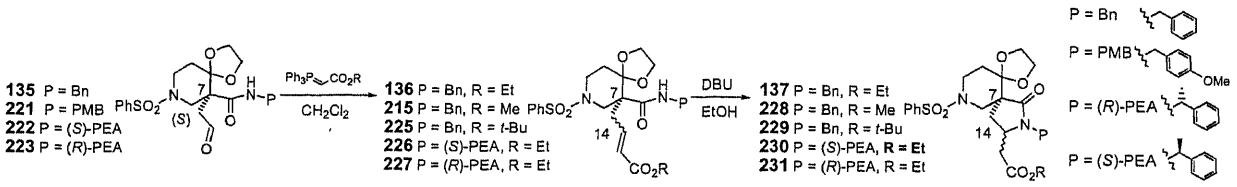
Scheme 36　スピロ-γ-ラクタムの合成



アルデヒド**135**が安定して得られるようになった結果、αβ不飽和エステル**136**の収率も向上した。なお、Wittig反応の*EZ*選択性は約4:1であった。

次に分子内マイケル環化反応[13]を検討した。特に**137**のH-14位のジアステレオ選択性が全合成において鍵となる。そこで分子内Michael反応におけるエステル側鎖，アミド側鎖，反応温度等のジアステレオ選択比に及ぼす効果を検討した(Table 4)。その結果、H-14位のジアステレオ選択性は、EtOH中ではH-14α:H-14β (4:1)，CH_2Cl_2中ではH-14α:H-14β (1:7)となった以外は選択性に大きな差は見られなかった。

Table 4　エステル誘導体およびアミド誘導体による分子内ﾏｲｹﾙ反応の検討



No	R	P	原料	反応溶媒	塩基(eq)	温度	反応時間	変換率	H-14α:β*1	ｺﾒﾝﾄ
1	Et	Bn	*E*	EtOH	DBU(1)	0 °C	7 h	96	79:17	
2	Et	Bn	*E*	EtOH	DBU(1)	rt	2 h	100	83:17	
3	Et	Bn	*E*	EtOH	DBU(1)	90 °C	72 h	100	83:17-80:20	
4	Et	Bn	*E*	THF	DBU(1)	rt	2 h	76	50:50	
5	Et	Bn	*E*	CH_2Cl_2	DBU(1)	rt	2 h	93	28:72	
6	Et	Bn	*Z*	CH_2Cl_2	DBU(1)	-30 °C	72 h	95	12:88	
7	Et	Bn	*Z*	EtOH	DBU(1)	rt	2 h	100	77:23	
8	Et	Bn	*E*: *Z* (79: 21)	EtOH	DBU(1)	rt	1 h	100	81:19-77:23	
9	Me	Bn	*E*: *Z* (84: 16)	MeOH	DBU(1)	rt	17 h	100	74:26	
10	*t*-Bu	Bn	*E*: *Z* (78: 22)	EtOH	DBU(1)	rt	24 h	95	78:22	残留原料*E*: *Z* (不明)
11	Et	PMB	*E*: *Z* (76: 24)	EtOH	DBU(1)	rt	24 h	100	76:24	
12	Et	(*S*)-PEA	*E*: *Z* (72: 28)	EtOH	DBU(1)	rt	24 h	100	78:22*2	原料は(7*R*)(*S*)-PEA
13	Et	(*R*)-PEA	*E*: *Z* (85: 15)	EtOH	DBU(1)	rt	24 h	100	80:20*2	原料は(7*R*)(*R*)-PEA

＊1　原料のEZ比，生成物のH-14αβ比，変換率は、^{1}H NMRより算出した。(不明)は、誤差が大きく算出不可を示す。

＊2　実際の実験は光学活性な7*R*体を使用したが、表記が煩雑になるため、7*S*体として記載した。

次にカラムクロマト精製の省略を目的にWittig反応の副生成物(トリフェニルホスフィンオキサイド)を分液除去することにした(Scheme 36)。即ち、エステル**137**をカルボン酸**217**へ加水分解し、逆抽出後、再度エステル化した。エステル**137**を$LiBH_4$還元後、ケタールを70%過塩素酸で酸化的に酸開裂し、酢酸エチル中懸濁攪拌すると目的のH-14α体**219**を単一の結晶として得た(Scheme 37)。不要なH-14β体**232**は14位側鎖と8位ケト基が分子内ケタールを形成した。その結果14位側鎖の立体配置がαと証明した。各ジアステレオマーの相対立体配置は両ジアステレオマーのnOeの比較から決定した(Fig. 3, Fig. 4)。

Scheme 37　脱ケタール化反応

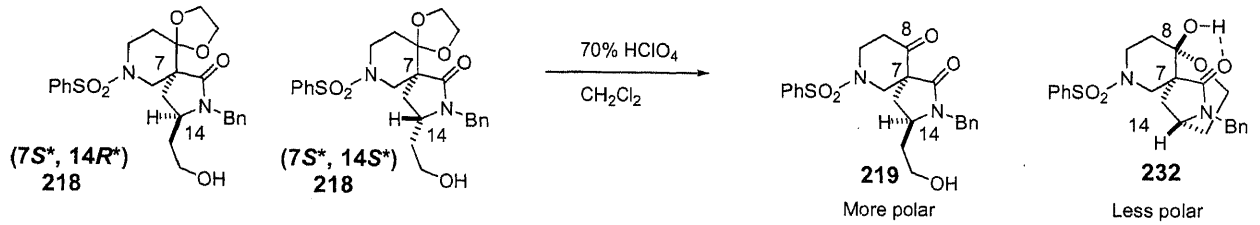
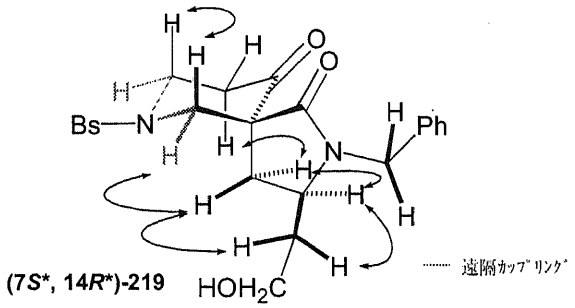
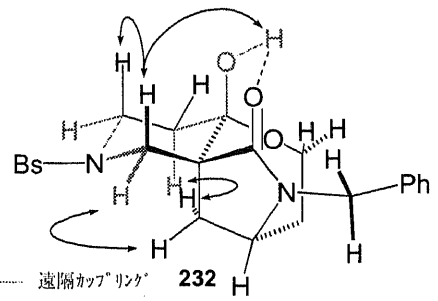


Fig 3　14位エピマーのnOe相関 H-14α体



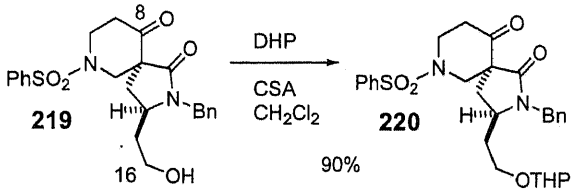
(7*S**, 14*R**)-219

Fig. 4　14位エピマーのnOe相関 H-14β体



次に酸性条件下にて**219**をテトラヒドロピラニル化[50] した(Scheme 38)。塩基性条件ではScheme 18のような8位エノレートと1級水酸基との掛け分けが必要である。しかし、酸性条件のため、1級水酸基の選択的保護が可能となった。また、酸性では、ケトアルコールの分子間ケタールの形成を抑え、選択的に目的のTHPエーテル**220**を簡便に得た。**220**は他のマンザミン誘導体の合成に適用可能な鍵中間体である。

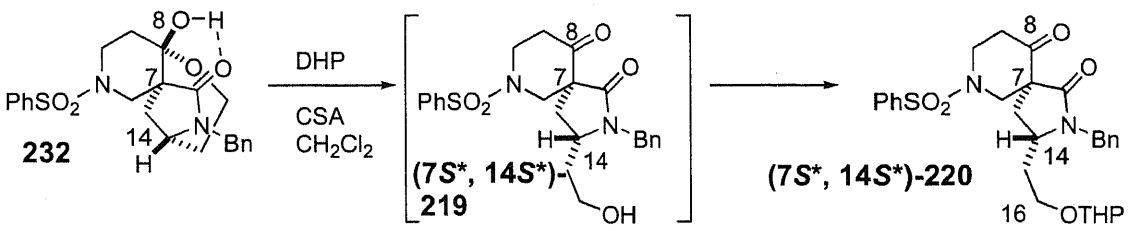
Scheme 38　THP化反応



以上、目的のスピロ-γ-ラクタム(7*S**,14*R**)-**220**が通算収率38.7% (14 steps)にて得られるようになった(Scheme 36)。

なお、H-14β体**232**は、分子内ケタールを形成しているが、同様に酸性条件では開環し、低級の水酸基からTHP化[51]されるため、1級水酸基が選択的にTHP体化された (7*S**,14*S**)-**220**が得られた(Scheme 39)。構造は、^{13}C NMRやIRにて8位ケト基が再生し、HMBCにてTHP H-2'からC-16位への$^{3}J_{HC}$のクロスピークを得た点から決定した。

Scheme 39　THP化反応

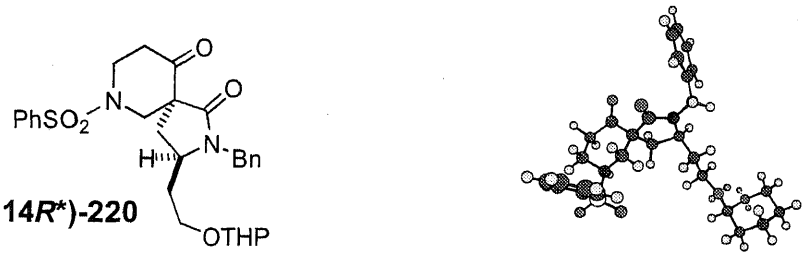


第二節　14位置換スピロ-γ-ラクタムの変換

次に残った官能基の8位ケト基をエノールトリフラート**233**[31] に変換した(Table 5)。このトリフラート**233**は、前駆体**220**(Fig. 5)で示すようにD環のベンジルラクタムが、THPオキシエチル側鎖にぶつからないように8位ケト側にせり出していると推定した。その結果、シ

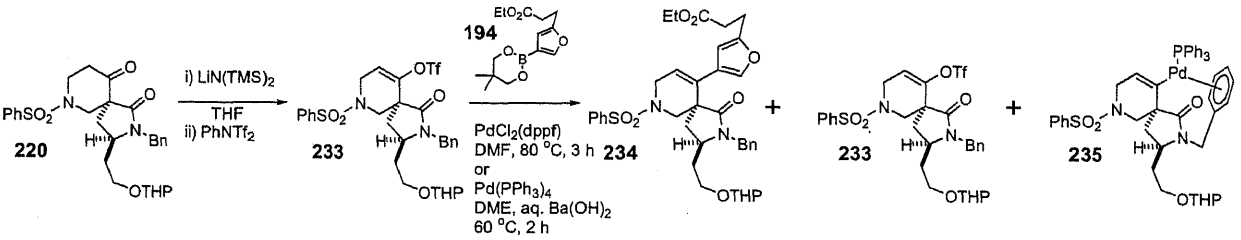
リカゲルカラムクロマト精製が容易な、安定なトリフラートを形成した(このため、後の鈴木カップリングでは立体障害の大きいケースとして強塩基を用いる必要があった)。

Fig 5　ケト体220のモデル図



次に鈴木カップリングを検討した(Table 5)。鈴木カップリング[Na_2CO_3, LiCl, $Pd(PPh_3)_4$]ではカップリング体**234**の変換率が48%と低かった。これは14位の側鎖がベンジルラクタム基をエノールトリフラートの向きにせり出させ、立体障害を起こしているためと考える(Fig. 5)。そのためカップリング速度が低下し、ネオペンチルボレート**194**が先に加水分解を受け、未反応のトリフラート体**233**が回収された。次に強塩基[32] である水溶性水酸化バリウムの系とリン酸三カリウムの系を比較した。その結果、トリフラート**233**が分解しにくいリン酸三カリウム系にて最高約95%にてカップリング体**234**が得られるようになった。

Table 5　鈴木カップリングの検討

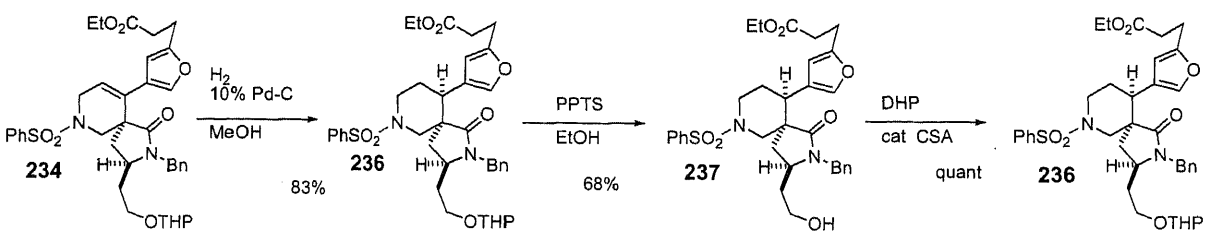


No.	Scale	Cat (5 mol%)	Base	sol		229	228	230
1	2.6 g	$Pd(PPh_3)_4$	Na_2CO_3 (3)	DME	80 °C, 3 h	48%	14%	16%
2	0.2 g	$Pd(PPh_3)_4$	$Ba(OH)_2$ (3)	DME	80 °C, 3 h	71%	non	non
3	11.2 g	$Pd(PPh_3)_4$	$Ba(OH)_2$ (3)	DME	80 °C, 3 h	65%	15%	---
4	0.2 g	$PdCl_2(dppf)$	K_3PO_4 (3)	DMF	80 °C, 3 h	81%	non	non
5	5.0 g	$PdCl_2(dppf)$	K_3PO_4 (3)	DMF	80 °C, 3 h	95%	non	non

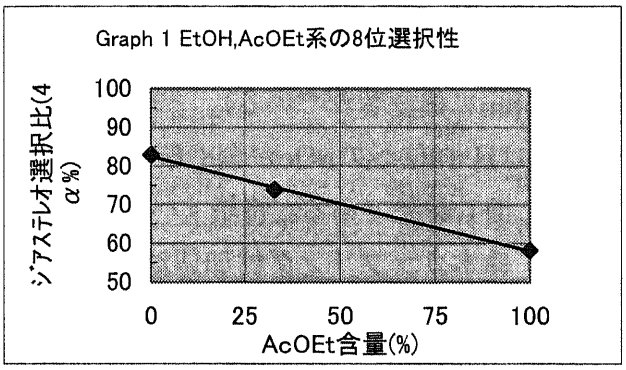
OTf化を含む2工程の収率

次いで8位をジアステレオ選択的に接触還元(H_2/10%Pd-C)した。モデル**159**の場合(Scheme 26)はH-8α:H-8βの選択比が9:1であったが、14位側鎖を有する**234**の場合はH-8α:H-8βの選択比は4.8:1に低下した。側鎖の影響にて選択性が低下する現象は、フラン環の2位についても言え、置換基の数が増加するとジアステレオ選択性が低下する傾向があった。そこでジアステレオ選択性の向上を目的に検討した(Graph 1, Graph 2, Graph 3, Table 6)。

Scheme 40　E環合成のための側鎖を有するAD環化合物の合成法検討



まず溶媒効果による選択性を比較した(Graph 2, Table 6)。その結果、溶媒のアクセプター(AN)数[52] の上昇によって8位ジアステレオ選択性が向上し、メタノール溶媒の際に選択性が向上した。これは、D環ラクタム-*N*に置換した保護基(Boc, Bn)が電子供与性置換基になると僅かにジアステレオ選択性が低下する傾向と相関していると考える。またフランに2位側鎖(酢酸エステル)が置換すると選択性が僅かに低下したため、フラン側鎖やD環ラクタムの立体の影響による因子と置換基の電子的な因子が影響するとも推測された。



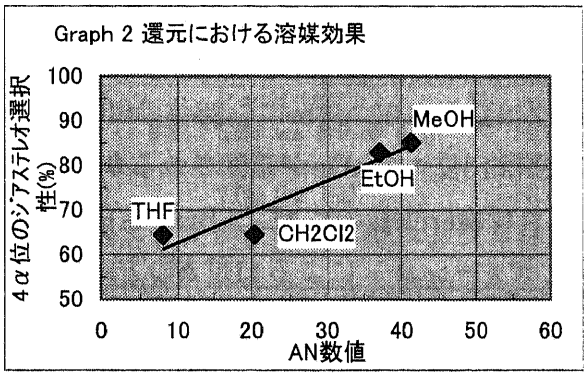
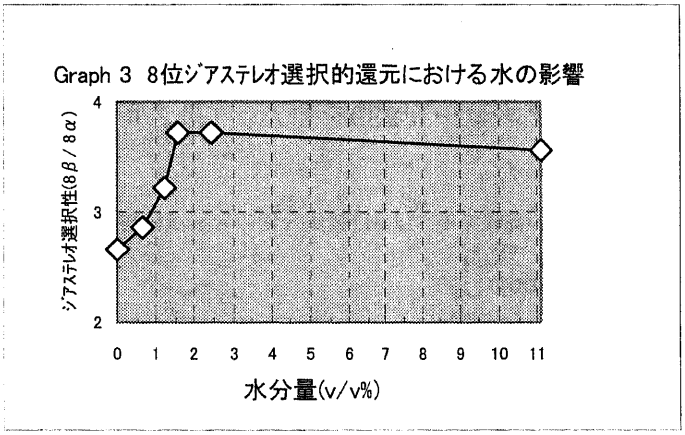


Table 6　接触還元時の8位のｼﾞｱｽﾃﾚｵ選択性

Run	Solvents	AN数	変換率	8α:8β	8α/β
1	MeOH	41.3	100%	85.2:14.8	5.76
2	EtOH	37.1	100%	82.9:17.1	4.85
3	$CHCl_3$	23.1	NR (2回実施)	---	---
4	CH_2Cl_2	20.4	100%	64.5:35.5	1.82
5	THF	8.0	100%	64.4:35.6	1.81
6	AcOEt	---	100%	58.2:41.8	1.39

ｱｸｾﾌﾟﾀｰ(AN)数 [52]--- 溶媒の電子受容性を表す尺度として^{31}P NMRの化学ｼﾌﾄに基づいた経験的ﾊﾟﾗﾒｰﾀｰ。ﾍｷｻﾝを一方の標準としてこれを0とし，1,2-ｼﾞｸﾛﾛｴﾀﾝ中の$Et_3P{=}O.SbCl_5$をもう一方の標準とし，これを100としたときの，ある溶媒中における$Et_3P{=}O$中の^{31}Pの相対的な化学ｼﾌﾄとして与えられる無次元の数として定義されている。$Et_3P{=}O$→Acceptor

しかし、**236**を合成をするうちに、10%-Pd/Cのロットが変わってしまった。 その結果、**236**のジアステレオ選択性が低下した。そこで8位のジアステレオ選択性を回復する検討が必要になった。触媒のロットの影響の一つに、触媒の含水率が予想された。そこで水の添加を検討した(Graph 3)。

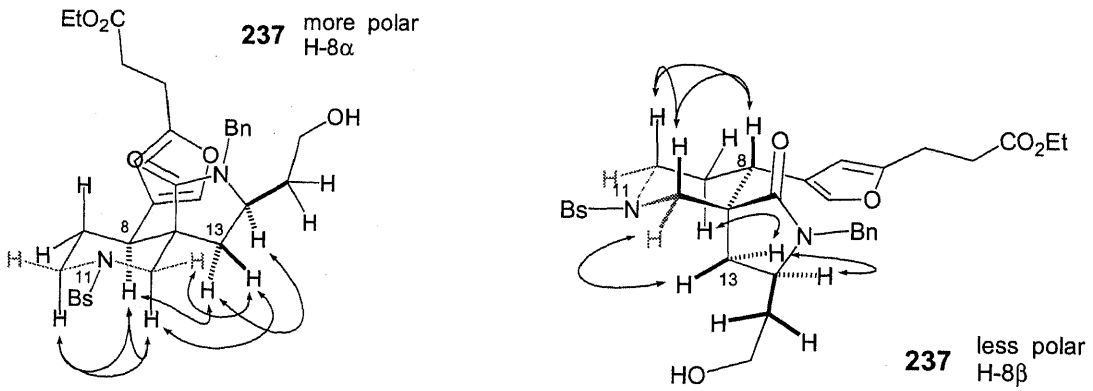


その結果、MeOH:H_2O (4:1)のときに最高値を示した。この条件にてスケールアップしたが

あまり効果が得られなかった。今後、酸や塩基等の添加物を検討する予定である。

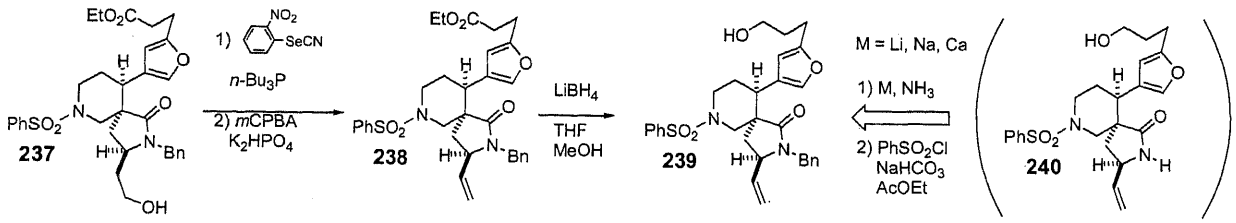
次に常法に従いPPTS/EtOH/50 °CにてTHPを脱保護し、アルコール体**237**まで変換した(Scheme 40)。回収した未反応のTHP体**236**から、H-8β体の方がH-8α体よりも脱THP反応が進行しやすいと判明した。更に脱THP化によって8位エピマーがシリカゲルクロマトで分離精製可能になった。そこで**237**の各ジアステレオマーを単離し、NOESYを測定した結果、8位の相対配置が完全に決定された(Fig. 6)。まずH-8α体の8位は^{1}H NMRで2.34 ppmに観測されるが、H-8β体の8位は^{1}H NMRで2.88 ppmへの低磁場シフトが観測された。この低磁場シフトはD環ラクタムの異方性効果に起因した(14位側鎖がない誘導体も同様に8α体の8位は1.93-2.03 ppmに、8β体の8位も2.78~2.85 ppmに確認されている)。また、H-8α体の8位は13位へのnOeが確認されるが、H-8β体の8位はH-13位へのnOeが全く観測されない。これはMerck社のK.M.J. BrandsらのnOe実験[4] と同じ結果である。特筆すべきはA環のコンホメーションによる11位*N*の方向である。即ち、鈴木カップリング付加体**234**(Scheme 40)以前ではマイナーな還元体異性体{(H-8β)-**237**}(Fig. 6)のようにA環が$_{11}$C^{8}のコンホメーションであるが、メジャーな還元体異性体{(H-8α)-**237**}(Fig. 6)ではじめてA環がフリップし、^{11}C$_{8}$のコンホメーションとなる。この際の11位*N*の方向が将来のF環の環化の方向を規制している。

Fig. 6　ｼﾞｱｽﾃﾚｵﾏｰのnOe相関図



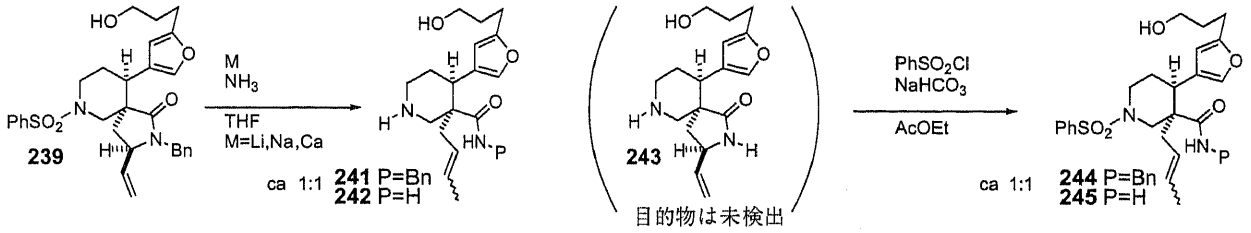
次に、8位エピマーの分離を目的にTHPを脱保護したため、14位側鎖を先にオレフィン**238**に変換した(Scheme 41)。即ち、1級アルコール**237**をトリブチルホスフィンとセレニルシアニドを用いてセレニルエーテル[53] とし、これを酸化的に脱離した。次いで2位側鎖のエステルを$LiBH_4$還元し、1級アルコール**239**を得た。1級アルコール体**239**は結晶であり、再結晶にて8位エピマーを除去した。

Scheme 41　E環合成のための側鎖を有するAD環化合物の合成法検討



次にD環ラクタムをアミナールに還元するにはラクタム-*N*に電子吸引性基が必要である。そのためBirch還元[54](M/NH_3/THF:M=Li, Na, Ca)にて**239**を脱ベンジル化した(Table 7)。

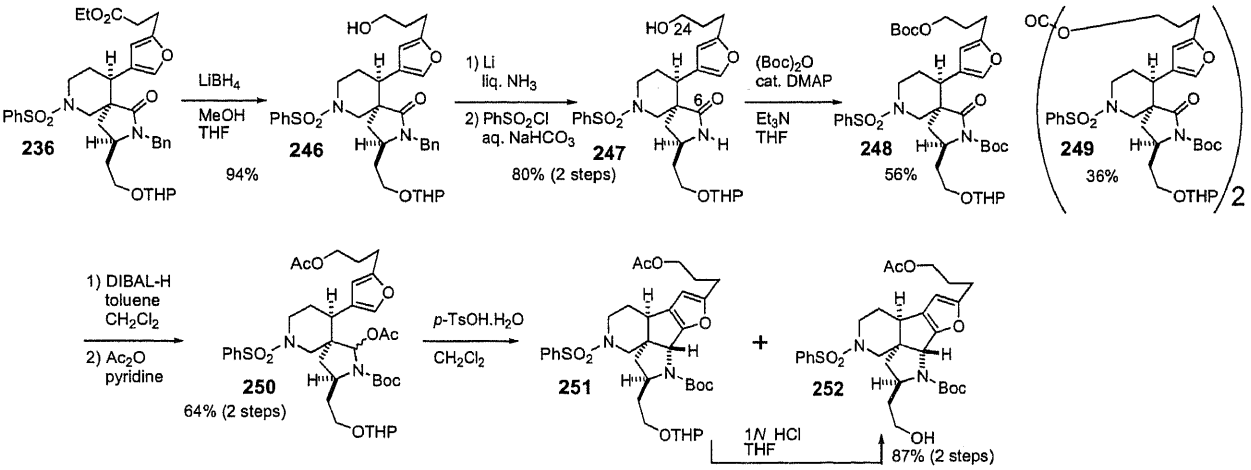
Table 7. Birch還元による脱Bn化の検討



No	M/NH_3	temp/time	変換率	P = Bn (*EZ* 比)	P = H (*EZ* 比)	脱ベンジル体
1	Li/NH_3/THF	−78 °C, 30 min	96%	44% (ca 8:9 or 9:8)	52% (ca 8:9 or 9:8)	ND
2	Na/NH_3/THF	−78 °C, 30 min	100%	100% (ca 1:1)	ND	ND
3	Ca/NH_3/THF	−78 °C, 60 min	100%	33% (ca 1:1)	77% (ca 1:1)	ND

その結果、ベンゼンスルホニル基は予想通りに還元除去されたが、目的の脱ベンジル体**243**でなく、立体障害の少ない末端アリルからの電子還元が優先したラクタムの開裂体**241,242**(*E*:*Z*比が約1:1)を与えた。このため、14位側鎖をオレフィンに変換した後にBirch還元に付すのでなく、Birch還元後に14位側鎖をオレフィン化するルートに変更した(Scheme 42)。まずTHP基は、脂溶性の向上および14位側鎖との区別を目的に残した。また2位側鎖がエステルだとBirch還元による脱ベンジル化でカルボン酸となるため、副生するチオフェノールとの分離やエステル化に手間がかかる。そこで**236**の2位側鎖のエチルエステル基を先に$LiBH_4$還元し、1級アルコール**246**を得た。次にBirch還元で脱ベンジル化した。予想どおり、Birch還元生成物はAcOEt抽出が可能であり、2*N* NaOH洗浄にて副生するチオフェノール等を容易に分液除去した。次に還元時に脱落したベンゼンスルホニル基をSchotten-Baumannにて再導入し**247**を得た。

Scheme 42 フラン誘導体の変換反応



次に6位を還元するために電子吸引性基のBocで保護した。過剰の$(Boc)_2O$を用い、D環ラクタム-*N*を定量的に保護し**248**を得た。その際、24位の1級アルコールがBoc化を受け、それが更に残りのアルコールに反応した2量体**249**を36%副生した。いずれもイミドとエステルを同時にDIBAL還元した後、無水酢酸・ピリジンにて24位水酸基とアミナールをアセチ

ル化し**250**を得た。次に塩化メチレン中、1当量の*p*-トルエンスルホン酸でイミニウムカチオン中間体を経た分子内環化反応に付し、14位に置換基を有する四環性化合物**251**を得た。その際、酸によってTHPが脱落した14位ヒドロキシエチル体**252**も得られた。THPが脱落しなかった**251**は1*N* HCl/THFにて選択的に脱保護し、収率80%で目的の14位ヒドロキシエチル体**252**に全て変換した。

今回、14位の置換基が影響し、フランの分子内環化の変換率が向上した。従来の14位が無置換のものでは*p*-トルエンスルホン酸によって分子内環化の前に脱Boc化した副生物が環化しないため、収率が約70%程度であった。今回は、B環の環化が完全に進行し、かつTHPが脱落したヒドロキシエチル体**252**も得られた。そのためBocのかわりにTHP基がスカベンジャーとなり、Boc基が残留したため、環化が効率よく進行したと推測された(Boc基が脱落しなかったため、環化体への変換率が向上した)。この脱THP体**252**の立体相関をNOESYで確認した(Fig. 7)。

Fig. 7　四環性中心骨格のnOe相関

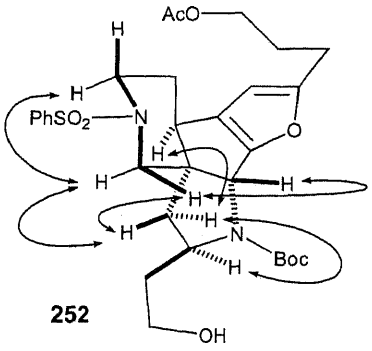
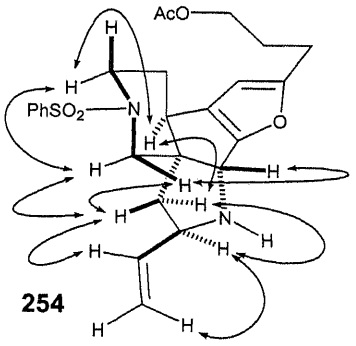
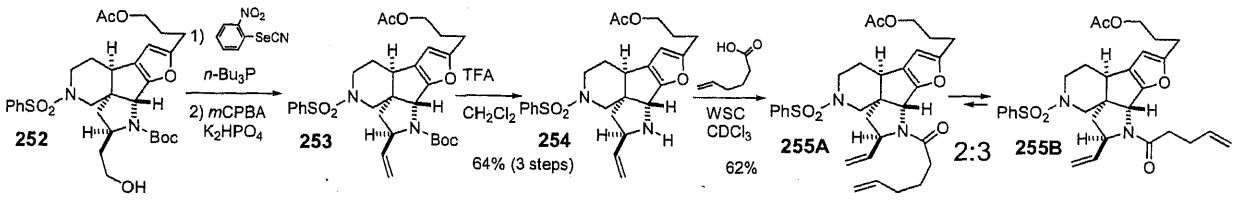


Fig. 8　四環性中心骨格のnOe相関



次に14位ヒドロキシエチル体**252**をセレニルエーテルに変換した後、酸化脱離にてオレフィン**253**に変換した(Scheme 43)。次いでTFA/CH_2Cl_2で脱Boc化[55]し、2級アミン**254**を得た。この2級アミン**254**は、Bocロートマーが消失したため、シャープなNMRシグナルを与え、NOESYにより立体化学を再確認した(Fig. 8)。

Scheme 43　フラン誘導体の変換反応

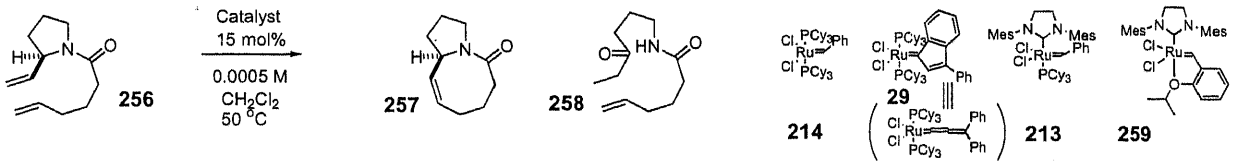


次に2級アミン**254**と5-ヘキセン酸をWSC・HCl/HOBtにて縮合し、アミドロートマー (2:3)を有するジエン**255**を得た。

次にRCM[20, 56]を検討した。まずプロリン誘導体**256**[57]をDE環のモデルとしてRCMを検討した(Table 8)。触媒**213**, **214**はStrem社 市販品を、触媒**29**は自家調製品[3c] を、触媒**259**

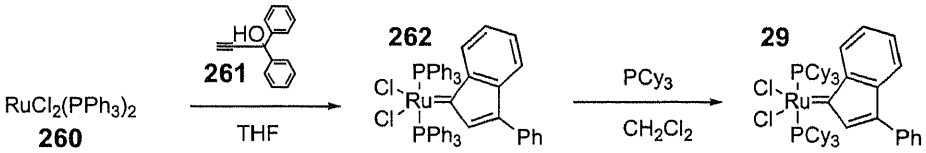
はAldrich社 市販品を用いた。

Table 8　DE環モデルのRCM



No	触媒	反応濃度	温度	時間	257	256	258	コメント
1	**214** (15 mol%)	0.001 M	50 °C	24 h	36%	50%	14%	他の副生物あり
2	**29** (15 mol%)	0.001 M	50 °C	24 h	36%	64%	trace	他の副生物あり
3	**213** (15 mol%)	0.001 M	50 °C	1.5 h	53%	35%	ND	
4	**259** (15 mol%)	0.001 M	50 °C	1.5 h	Major	trace	ND	
5	**259** (15 mol%)	0.001 M	50 °C	24 h	59%	41%	ND	

触媒29は、Fürstnerの文献[3c]に従い調製した。

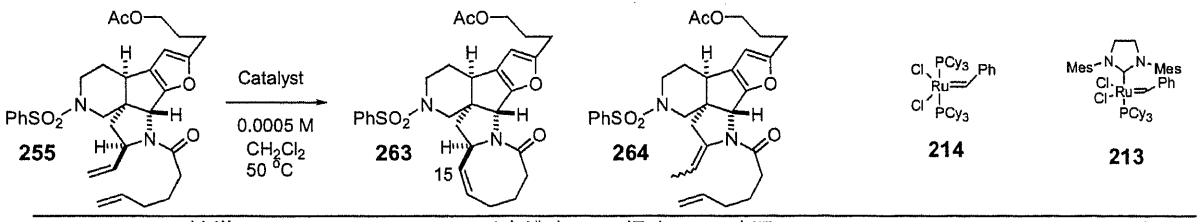


その結果、触媒**214**, **29**では、ビニル基の異性化を経て生成したエナミンが開裂した開環体**258**を副生した。反応時間も長く、8員環の生成効率は悪かった。

それに対して触媒**213**では異性化反応が抑制され、原料**256**と目的の**257**以外は確認できなかった。触媒**259**では触媒**214**, **29**のときより反応が速いが、触媒**213**のときよりははるかに遅かった。しかし、異性化は認められなかった。

そこで触媒**213**を目的の四環性化合物**255**に適用した。その結果、触媒**213**を用いると目的の五環性化合物**263**が得られた(Table 9)。その構造は、環化前の基質**255**にあったアミドロートマーがRCM後には解消されている点, オレフィンのJ値(11.9 Hz)から15*Z*-構造が支持された。なお、15*E*-体は観測されなかった[58]。念のために触媒**214**も検討したところ目的の**263**以外にエナミン**264**が得られた。

Table 9　四環性化合物のRCM

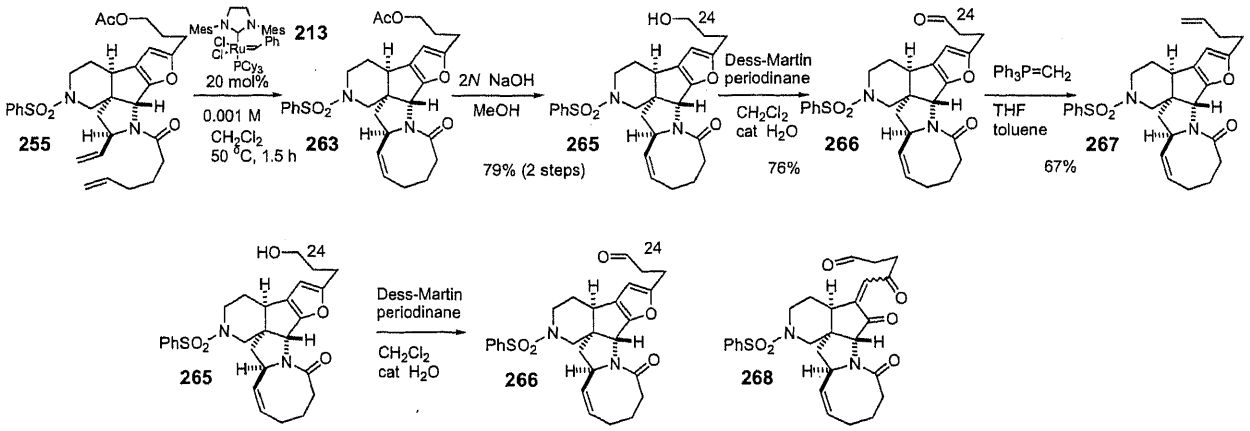


No	触媒	SM	反応濃度	温度	時間	263	255	コメント
1	**214** (15 mol%)	83 mg	0.0005 M	50 °C	72 h	4%	64%	**264** (5%)
2	**214** (30 mol%)	53 mg	0.0005 M	50 °C	72 h	15%	trace	many spots
3	**214** (30 mol%)	100 mg	0.0005 M	50 °C	48 h	15%	30%	many spots
4	**213** (20 mol%)	24 mg	0.001 M	50 °C	1.5 h	55%	trace	ND
5	**213** (20 mol%)	360 mg	0.001 M	50 °C	1.5 h	86%	11%	ND

次にアセチル基を塩基性加水分解して1級アルコール**265**とし、Dess-Martin酸化[39b] しアルデヒド**266**とした(Scheme 44)。Dess-Martin酸化において水を添加するS.L. Schreiberらの改良法[39a] を用いたところ、少過剰のDess-Martin試薬がフラン環の酸化開裂を招いて

ジオキソ体**268**を副生したため、Dess-Martin試薬を1当量以内に抑える点が重要であった。

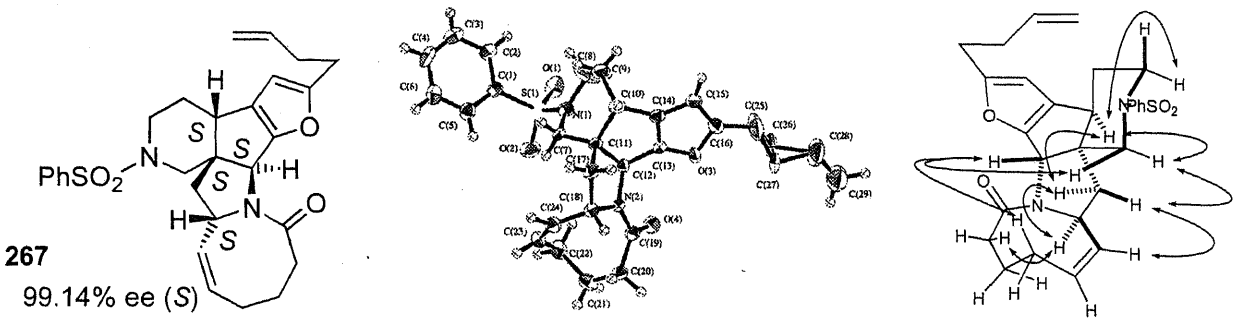
Scheme 44　フラン誘導体の変換反応



次にWittig反応にて末端オレフィン**267**を得た。Wittig反応ではリンイリドの発生にカリウムシリルアミドを用いたが、過剰の塩基は23位-アルデヒドをエノール化するため少なめに使用しないと収率が低下した。ここで得た末端オレフィン体**267**は、5環性中間体の中で、最も脂溶性が高い結晶であり、4工程前のRCMのルテニウム残渣の除去が可能となった。また脂溶性が高いため、後の順層のキラルHPLC分析においても分析濃度があげられ、光学純度の正確な判定を可能にした重要な鍵中間体であった。

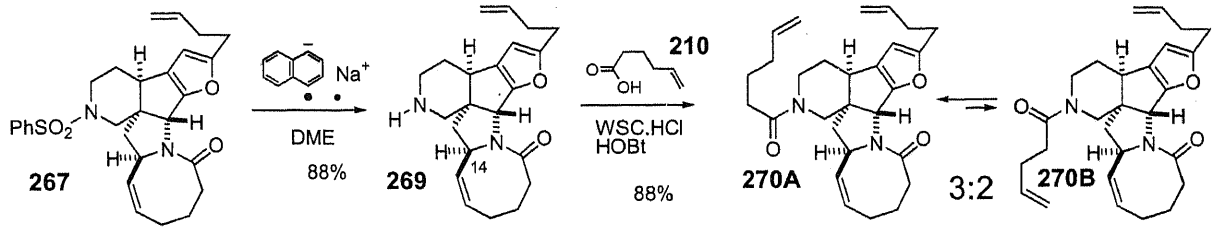
また後の検討にて5環性化合物**267**[(*S*)-(-)体]の単結晶をエタノール再結晶にて得た(Fig. 9)。この単結晶のX線結晶構造解析では、23位にdisorderが観測されたが、6,7,8,14位が目的の立体構造を有すると確認・決定した。これらの立体相間はNOESYの結果を支持した。ここで興味深い点はABC環の平面構造に対してA環のNがD環とantiの位置関係にあり、将来F環が環化する方向を制御するのに役立っている点である。

Fig. 9　20,29-ジオキソナカドマリン Aの合成



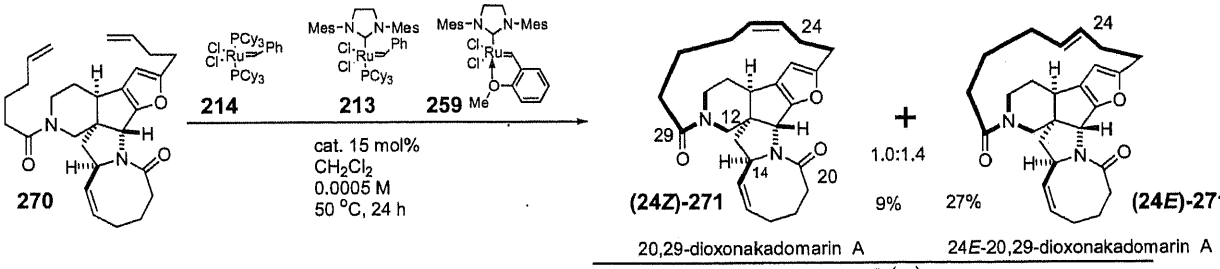
次にベンゼンスルホニル基をNa-ナフタレンで還元的に除去[41]し、更に副生する過剰のナフタレン等を塩酸の逆抽出によって除去し、簡便に2級アミン**269**を得た(Scheme 45)。2級アミン**269**と5-ヘキセン酸**210**を再度WSC・HCl/HOBtにて縮合し、ジエン**270**を得た。

Scheme 45　20,29-ジオキソナカドマリン Aの合成



得られたジエン270のRCMを検討した。その結果、イミダゾリル配位子を有する触媒213, 259では環化体以外に、2量体と推定される副生物(分離が困難)を多量に副生した。しかし、第1世代Grubbs試薬214によるRCM (20 mol%, 0.0005 M, 50 °C, 24 h)では目的の環化が進行し、20,29-ジオキソナカドマリンA 271を与えた。24位の*Z*:*E*比は1.0:1.4 (41:59)であり、モデル実験(38:52)と同等であった。

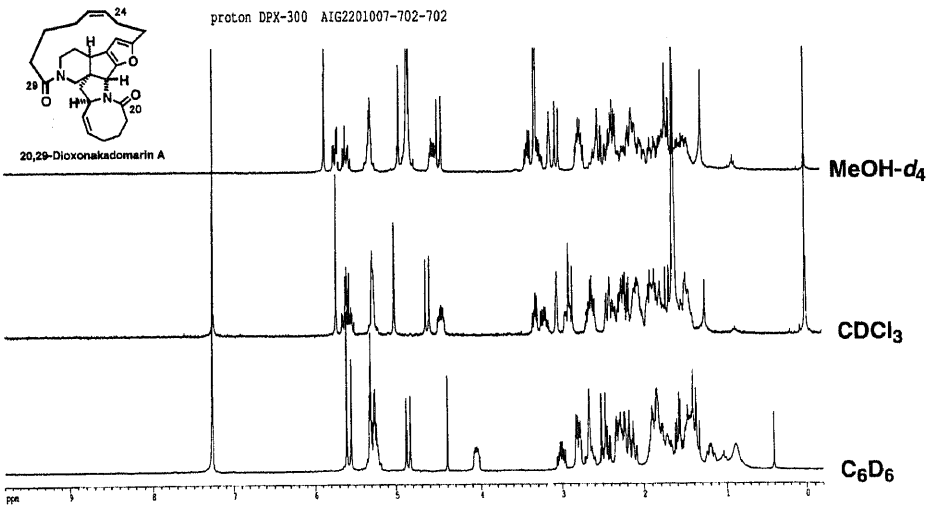
Table 10　四環性化合物のRCM



No.	Catalyst	Substrate	time	Yield (%) (24*Z*)-271	(24*E*)-271	dimer	270
1	**214** (15 mol%)	0.0005 M	24 h	26%	40%	ND	ND
2	**213** (15 mol%)	0.0005 M	2 h	11%	1%		ND
3	**259** (15 mol%)	0.0005 M	24 h	7%	22%		ND

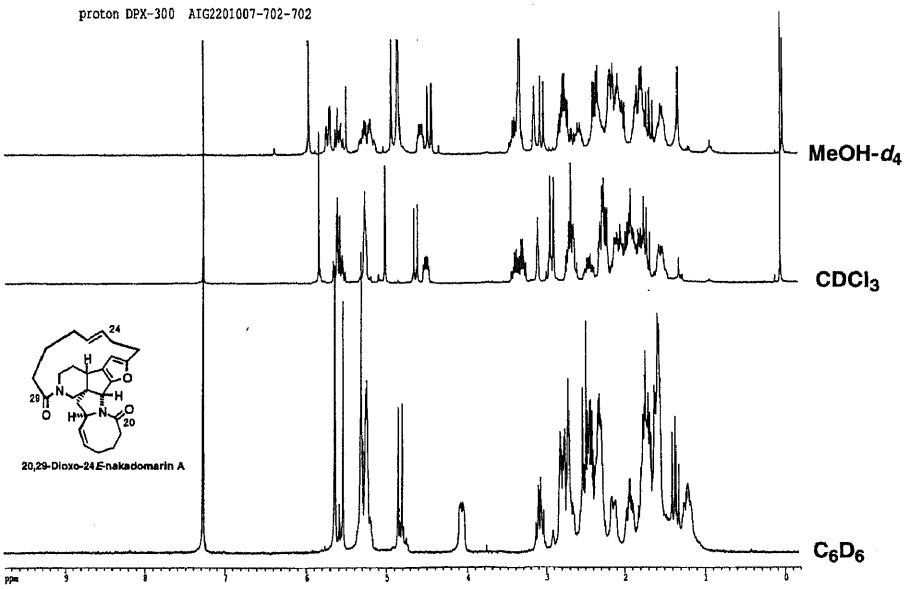
20,29-ジオキソナカドマリンA 271の閉環構造は、270の11位-アミドロートマーが、RCM後に解消された点からも支持された。また29位アミドのカルボニル基は、H-12eqが異方性効果によって大きく低磁場シフトしていたためモデル化合物と同様、カルボニル基がH-12eq側に向いていると判明した。24位の立体配置は、^{1}H NMR (MeOH-d_4)での結合定数から帰属した($CDCl_3$中の^{1}H NMRではbrmのため、判別はできなかった)(Chart 1, Chart 2)。

Chart 1　24*Z*-20,29-ジオキソナカドマリンAの^{1}H-NMR



271の幾何異性(24位)は、*E*体が^{1}H NMR (MeOH-d_4)で大きくカップリング(分解能の問題でJ値は読み取れなかった)していた点以外は、他の測定溶媒中でも、*Z*体の測定でもbrmであり、J値の判別に至らなかった(後の構造変換にてJ値から決定できた)。

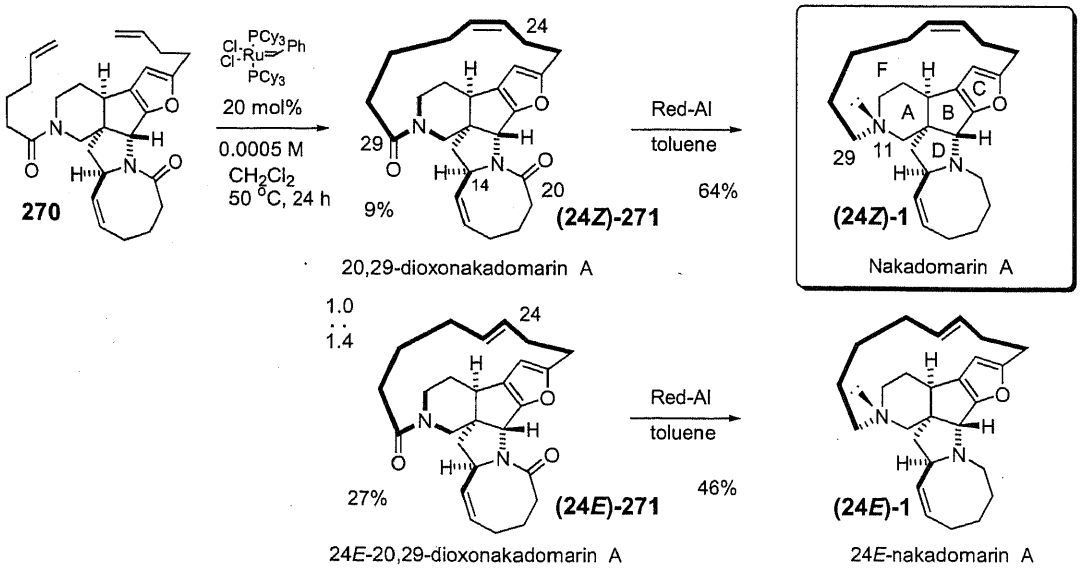
Chart 2　24*E*-20,29-ジオキソナカドマリンAの^{1}H-NMR



次に20,29-ジオキソナカドマリンAと24*E*-20,29-ジオキソナカドマリンAをそれぞれRed-Al還元[59]し、ナカドマリンAと24*E*-ナカドマリンAを得た(Scheme 46)。

合成したナカドマリンA(ラセミ体)の構造は、次章の最後にて天然物との比較と同時にまとめて詳細に述べる。結論だけ先に述べると、相対配置が*R**体(6*R**, 7*R**, 8*R**, 11*R**, 14*R**)の場合、従来提唱されていたABCDE環の構造に加え、今回、合成によってはじめてF環がABC環面に対してβ側、即ちD環と*trans*の位置関係にあると決定した。即ち、ナカドマリンAの11位N-29位C結合が破線のβ側(equatorial側)に、11位Nの非共有電子対がα側(axial側)になっているがF環はABC環面に対してβ側を示しているため、下記のように表記した。

Scheme 46　20,29-ジオキソナカドマリン Aの合成



第四章　光学活性ナカドマリンAの不斉全合成

第一節 鍵中間体の光学分割

前章までにナカドマリンA(ラセミ体)の全合成が完了した。そこで、次にナカドマリンA(天然由来)の絶対構造を決定する目的で光学活性ナカドマリンAの合成を開始した。まず光学活性体を合成するには以下の四点を確認する必要があった。

1. 各合成中間体のキラルHPLC条件の設定
2. 光学活性体とラセミ体の物性の把握
3. 確実に99% ee以上の光学純度にできる鍵中間体の設定と確保
4. ラセミ化工程や精製によって光学純度が低下する工程を把握した合成ルートの設定

即ち、

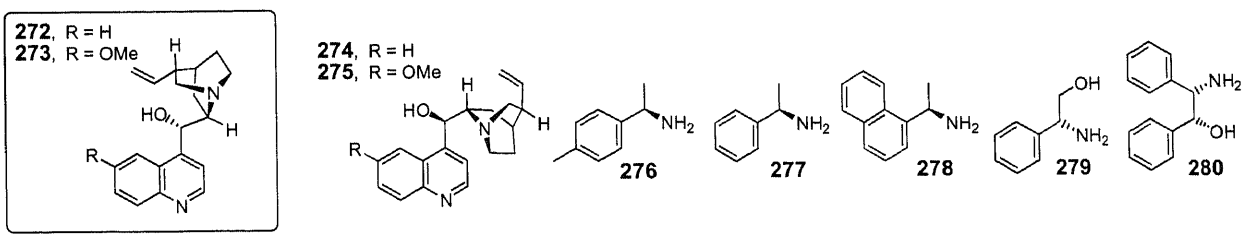
第1点について---各合成中間体のラセミ体(標品)を用い、キラルHPLC条件を探索した。その結果、カルボン酸誘導体はCHIRALPAK AD[ダイセル化学工業(株)]の移動相にTFAを添加した条件にて、他の誘導体はCHIRALPAK AD[ダイセル化学工業(株)]を加温下(40 °C)にて溶出する条件にてピークが完全に分離した。中でもスピロラクタムや五環性化合物の分離は良く、分析カラムでのmgオーダーの分取が可能なほど完全に分離した。

次に、

第2から4点について---得てしてラセミ体は結晶でも光学活性体はアメ状である化合物が多い。そこで難溶性結晶のラセミ中間体の光学分割(ジアステレオマー塩法)を検討した。近年、光学活性体の不斉合成は種々報告され、天然物合成に応用されているが、100% ee近く完全に制御できる不斉合成法は少なく、光学純度が低い場合は結局、光学純度を確実に上げる必要がある。そのため、鍵中間体にて光学純度を確実に上げるために光学分割(ジアステレオマー塩法)を優先して検討した。

まず比較的入手の容易な光学活性塩基(12種)とカルボン酸**133**(ラセミ体)を塩化メチレンに完全に溶解して有機塩を形成させた後、CH_2Cl_2/*n*-hexane, AcOEt, AcOEt/*n*-hexane, AcOEt/IPE, Et_2O, EtOH, MeOHの条件(溶媒, 温度)にて結晶が析出する系を探索した。その結果、類似構造(アミノアルコール)を有するシンコニン**272**とキニジン**273**が、メタノール中、カルボン酸**133**と1:1の光学分割が可能なジアステレオマー塩を形成した。なお1:1の比は^{1}H NMRと元素分析にて算出した。

Fig. 10　中間体(ｶﾙﾎﾞﾝ酸)の光学分割(ｼﾞｱｽﾃﾚｵﾏｰ塩法)



次にシンコニン塩 [溶解度: 0.58 w/w% (MeOH), 0.15 w/w% (EtOH)] と キニジン塩 [溶解度: 1.05 w/w% (MeOH), 0.89w/w% (EtOH)]の溶解度を測定した結果、キニジン塩のほうがメトキシ基のために溶解度が高く比容積が大きかった。そのため室温での溶解度・操作性・比容・回収率 が優れていたシンコニン塩について分割条件を至適化した。その結果、シンコニン**272**とカルボン酸**133**を1:1の比で混合し、メタノールから結晶化し、複分解すると(*R*)-(-)-カルボン酸[(*R*)-**133**](アメ状物)が99.6% ee, 通算収率38.9%(最高収率50%と換算)で得られた(Scheme 47)。なお、シンコニン塩が99% deよりも低い場合は、より溶解しにくいEtOHから再結晶すると回収率良く光学純度を上げられ、カルボン酸**133**を確実に 99% ee (*R*)以上で得られるようになった。また、カルボン酸**133**の絶対配置は、シンコニン塩のX線結晶構造解析[60]から(7*R*)-(-)-体と決定した(Fig 11)。

Scheme 47　中間体(ｶﾙﾎﾞﾝ酸)の光学分割(ｼﾞｱｽﾃﾚｵﾏｰ塩法)

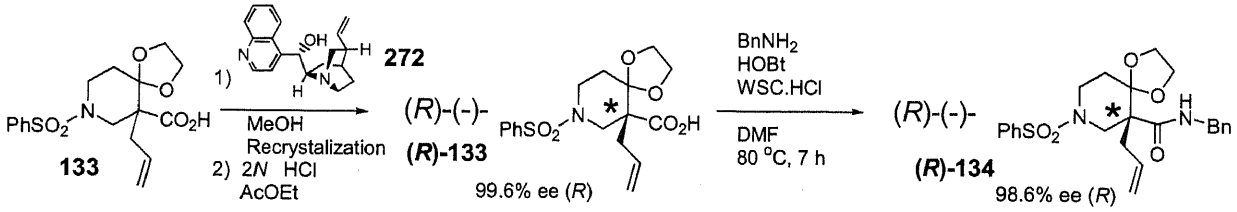
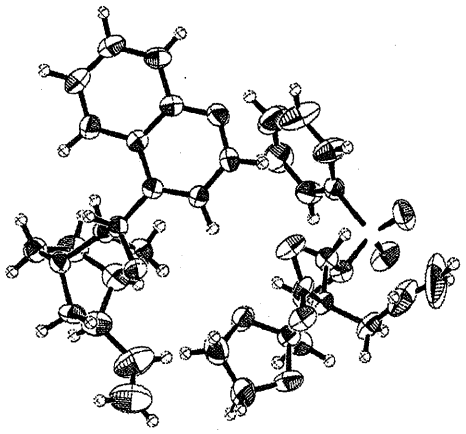


Fig. 11　シンコニン塩のX線結晶構造解析のORTEP図



(*R*)-(-)-カルボン酸[(*R*)-**133**]は、アメ状物で操作性が悪いため、WSCにて結晶の(*R*)-(-)-ベンジルアミド**134**に変換した(Scheme 47)。光学活性ベンジルアミド**134**は、エーテル系以外の溶媒に、ラセミ体結晶の溶解度が光学活体結晶の溶解度よりも低いため[61]、ろ取による回収率を上げる点が重要であった。しかし、僅かに光学純度(約1% ee)をﾛｽし、98.6% eeに低下した。

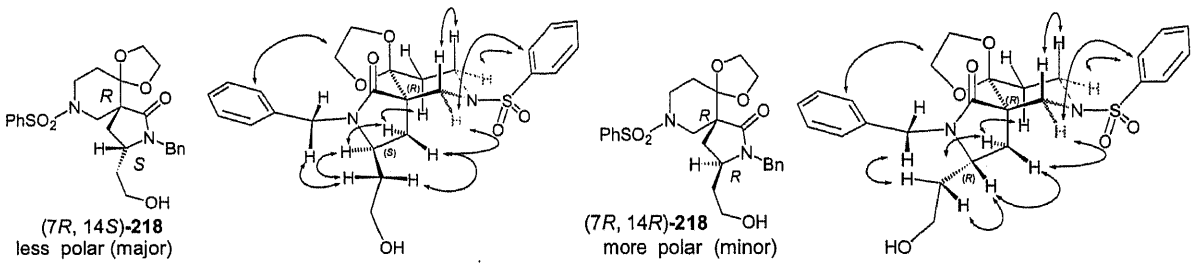
以上の操作にて7位不斉点の光学分割が可能になった。続いて、(*R*)-(-)-カルボン酸から得られるベンジルアミド**134**を光学活性ナカドマリンAに誘導することにした。

第二節 光学活性スピロ化合物の合成と(*S*)-(+)-ナカドマリンAの不斉全合成

結晶性の光学活性ベンジルアミド **134** を得た。そこでラセミ体の合成ルートに従って変換

した(Scheme 48)。はじめにアリル基を四酸化オスミウム酸化してジオールとした後、過ヨウ素酸ナトリウムにて酸化開裂してアルデヒド**135**とした。速やかにWittig反応に付してαβ不飽和エステル**136**とし、DBUにて分子内Michael反応に付してスピロラクタム**137**を得た。ここまでの操作ではWittig反応残渣等の不純物を含むため、16位-エステルを加水分解して逆抽出にて精製した。エタノール中、アセチルクロライドを滴下し、エステル化した。次に$LiBH_4$還元し、不要なH-14位エピマー**218**[(7*R*,14*R*)-体]をカラムクロマト精製にて除去した。**218**の両ジアステレオマーの光学純度は[(7*R*,14*S*)-体:(7*R*,14*R*)-体 98.9% ee, 96.5% ee]であった。次工程の精製は困難なため、この時点での精製は重要であった。単離した両異性体**218**の立体化学をNOESYにて確認した(Fig. 12)。

Fig. 12　中間体(ｶﾙﾎﾞﾝ酸)の光学分割(ｼﾞｱｽﾃﾚｵﾏｰ塩法)

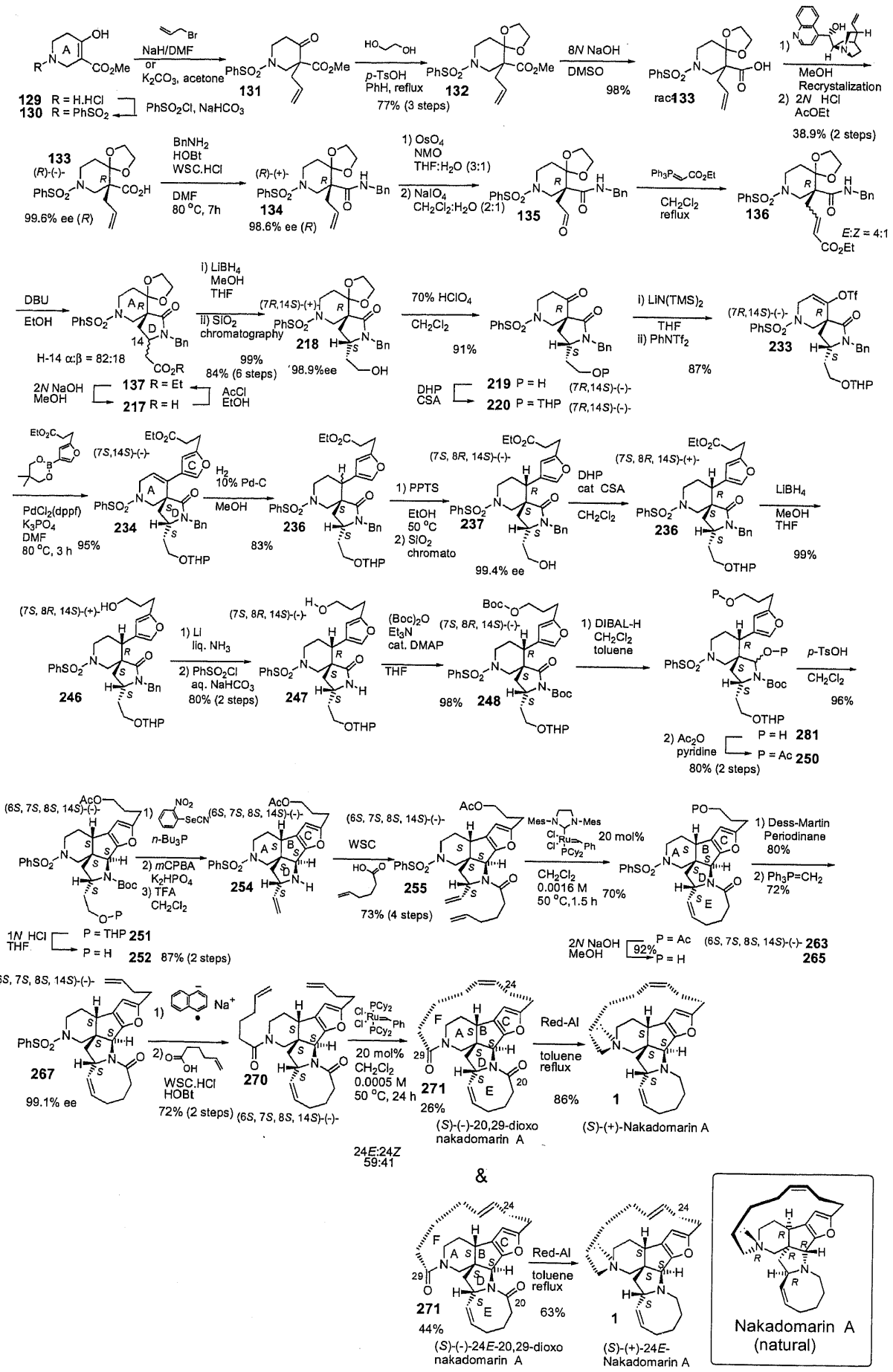


次いでケタール**218**を70%過塩素酸にて酸化的に酸開裂すると8位-ケト体**219**が得られた。ラセミ体ではこの8位-ケト体**219**が酢酸エチル中懸濁攪拌にて結晶化し、14位-エピマーとの分離を容易にした。しかし、光学活性体では8位-ケト体がアメ状であり、シリカゲルの弱酸にて16位-アルコールと8位-ケト基が一部分子間アセタールを形成し、複雑となった(他にも、先の副生物をプレパラ精製にて単離しても目的の8-ケト体に戻ったため、フリーの1級アルコールがシリカゲルの弱酸によって8位-ケト基に分子間で求核付加したものと推定した)。そこで触媒量のカンファースルホン酸とジヒドロピラン(DHP)を用い、酸性条件下、分子間アセタールの平衡をテトラヒドロピラニルエーテル側に非可逆的に傾け、高選択的に1級水酸基を保護し、単一のTHPエーテル**220**を得た。このような酸性条件での保護が操作の簡略化に重要であった。それは塩基性条件にて保護すると、モデル化合物**152**(Scheme 18)のように8位-ケト基との保護の競争になり、スケールアップの際のカラムクロマト精製に労力を要するためである。次に常法に従いトリフレート**233**に変換した。トリフレート化では塩基を過剰に添加すると逆Dieckman反応にてA環が開裂するため、注意を要した。

次にラセミ体の合成のときと同様に鈴木カップリングにつづく接触還元に付した。ここで生成した8位エピマー**236**[8*R*:8*S* (4:1)]は、エタノール中、PPTSにてTHPエーテルを開裂し、カラムクロマト精製にて目的の(7*S*, 8*R*, 14*S*)-体**237**を単離精製した (Chiralpak AD 99.4% ee)。

再度THP化し、24位エステルをテトラヒドロホウ酸リチウム還元にて1級アルコール**246**とした。次にベンジルラクタムをBirch還元にて脱保護した。その際、ベンゼンスルホニル

Scheme 48 (*S*)-ナカドマリンAの不斉全合成



基も脱保護されるため、再度保護し**247**を得た。フラン側鎖とD環ラクタムをBoc化後、DIBAL還元した。1当量の*p*-トルエンスルホン酸にてイミニウムカチオン中間体を経る分子内環化反応に付した後、THPを脱保護し、(6*S*, 7*S*, 8*S*, 14*S*)の四環性化合物**252**を得た。セレニルエーテル化後、酸化脱離にてオレフィンとした。次にBoc基をTFAにて脱保護し、**254**の立体化学をNOESYにて確認した。

5-ヘキセン酸と縮合し、RCMにてcis選択的にアゾシン環**263**を構築した。24位-アセチルエステルを塩基性加水分解し、1級アルコール**265**とした。Dess-Martin酸化につづくWittig反応にて(6*S*, 7*S*, 8*S*, 14*S*)のオレフィン**267**を得た(Chiralpak AD 99.1% ee)。**267**の相対配置は、X線結晶構造解析にて決定した(Fig. 9)。

次にベンゼンスルホニル基をNa-ナフタレンにて還元除去し、WSCにて5-ヘキセン酸と縮合し、**270**を得た。RCMに付し、24*Z*-20,29-dioxonakadomarin Aと24*E*-20,29-dioxonakadomarin Aを得た(Chiralcel AD >99% ee)。それぞれのビスラクタムをRed-Al還元し、(6*S*, 7*S*, 8*S*, 14*S*)-(+)-ナカドマリンA [*ent*-ナカドマリンA]の不斉全合成を達成した(Chiralcel OD >99% ee)。

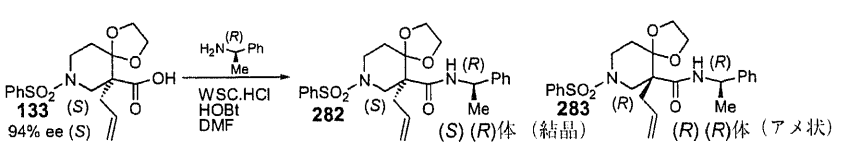
次に旋光度を測定した結果、(-)-ナカドマリンA (天然由来)は、(6*R*, 7*R*, 8*R*, 14*R*)の絶対配置を有すると決定した。この最終のナカドマリンAの構造決定は第四節にて詳細に述べる。

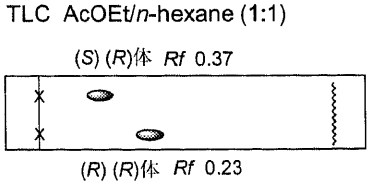
第三節 (*R*)-(-)-ナカドマリンAの形式不斉全合成

前節では、(*R*)-カルボン酸**133**を用い、(*S*)-(+)-ナカドマリンAを不斉全合成した。次に(*R*)-(-)-ナカドマリンA(天然型)を合成するには、99% ee以上の(*S*)-カルボン酸**133**が必要である。しかし、光学分割剤であるシンコニンの対掌体が市販されていないため、(7*S*)-(+)-カルボン酸**133**は、析出したシンコニン塩をろ別する方法にて光学純度を上げるしかなく、94% ee (*S*)が限界である。そこで、ジアステレオマーアミド法にて光学純度を上げることにした(Scheme 49)。

シンコニン塩を複分解後に(*R*)-(+)-α-メチルベンジルアミンと縮合 (WSC・HCl/HOBt/80 ℃)し、ジアステレオマーアミド**282**の結晶化にて(7*S*)体を99.9% de以上にて得た。このアミドは、カラムクロマトによる分離も可能であるが、酢酸エチル/IPEによる結晶化により、容易に約100% deの結晶に精製した。

Scheme 49　中間体(ｶﾙﾎﾞﾝ酸)の光学分割(ｼﾞｱｽﾃﾚｵﾏｰｱﾐﾄﾞ法)

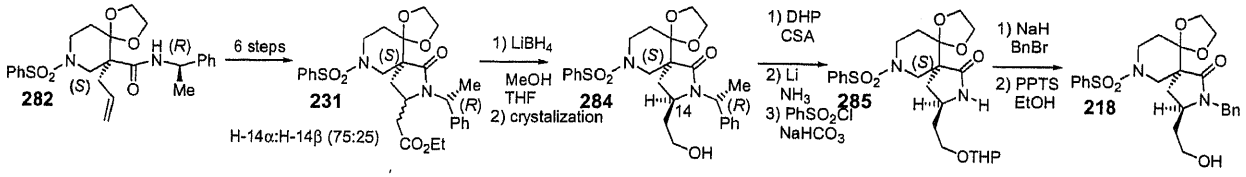




この(*R*)-α-メチルベンジルアミドを加水分解し、(7*S*)-カルボン酸が得られれば、先の(7*S*)-

カルボン酸133を原料とした(*R*)-(-)-ナカドマリンAの不斉合成が可能になる。そこで(7*S*),(*R*)-アミド282を、酸性・塩基性での加水分解を検討した。しかし、立体障害と反応性の低さからアミドの加水分解は全く進行しなかった。逆に脱ケタール化や末端アリル基が異性化した複雑な混合物を与え、(7*S*)-(+)-カルボン酸133は全く得られなかった。そこで(7*S*)体を、Birch還元による脱フェニルエチル化にて先の不斉合成ルートに合流させることにした(Scheme 50)。

Scheme 50　中間体(ｶﾙﾎﾞﾝ酸)の光学分割(ｼﾞｱｽﾃﾚｵﾏｰｱﾐﾄﾞ法)



スピロ-γ-ラクタム231への変換は既に分子内マイケル環化の検討にて確認済みである。これを$LiBH_4$還元にて1級アルコール284とした。このアルコール284は結晶であり、結晶化にて容易にH-14β体を除去できた(従来のベンジルラクタム体ではアメ状のためカラムクロマト精製を要する)。次いで1級アルコール284をTHPにて保護した(THP化しないとBirch還元後に水溶性になるため)。次いでBirch還元にて脱フェニルエチル化し、同時に脱落したベンゼンスルホニル基を再度保護した。ラクタム285をベンジル化後、THPを脱保護し、ナカドマリンAの不斉合成ルートに合流させた。218の光学純度は、99.5% ee (*S*)以上であった。この合成ルートではラセミ化しないことを実証済みのため、(*R*)-(-)-ナカドマリンAの形式不斉全合成を達成したことになる。

第四節 ナカドマリンA(天然由来)の同定と絶対構造の決定

以上より、ナカドマリンAの不斉合成を達成した。ナカドマリンA(合成品)の構造は、^{1}H NMR (600 MHz, MeOH-d_4)にて*N*近傍の炭素の線幅が広がった点[62]、二つのメチレンプロトンの生成からアミン構造とF環の渡環構築を確認した。また、鍵の24位の幾何異性の決定は、以下の様に決定した。

即ち、24*E*の決定は、MeOH-d_4溶媒中での^{1}H NMRにおいて24,25位プロトンが分離しなかったため、ピークが完全に分離するC_6D_6溶媒中での^{1}H NMRの結合定数(J = 14.9 Hz)から決定した。

24*Z*の決定は、MeOH-d_4溶媒中での^{1}H NMRにて24,25位プロトンが分離し、その結合定数(J = 10.9 Hz)から決定した($CDCl_3$中の^{1}H NMRではbrmのため、判別はできなかった)。

更にNOESY, 差nOeを詳細に検討すると、ナカドマリンA(合成品)のF環は27位と橋頭位6位間のnOeから、ABC環面に対してβ側と決定できた(Chart 3)。ABCDE環は既にX線結晶構造解析にて立体構造を確認済みのためこの時点で提唱されたナカドマリンAの構造[1a]は

合成されたと考える。F環がβ側から閉環したのはA環のコンホメーションが大きく影響したと考える。

次にナカドマリンA(天然由来)のデータ、即ち小林らのJOC(1997)[1c]のSupporting Informationのデータ(Chart 4)を確認すると同様にNOESYにて27位-6位間にnOeのクロスピークが観測されていることからF環がβ側から閉環していると判明した。

Chart 3　ﾅｶﾄﾞﾏﾘﾝA(合成品)の差nOe

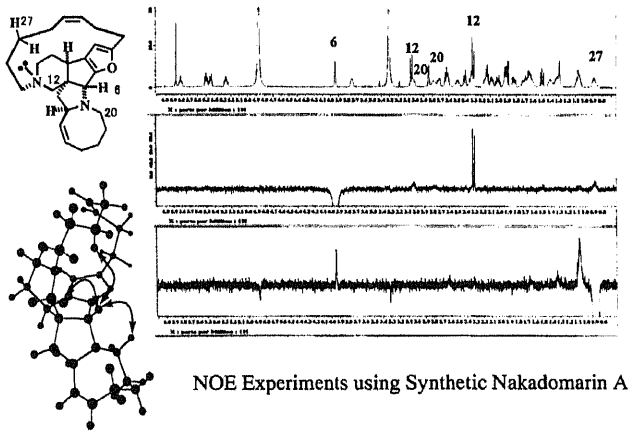
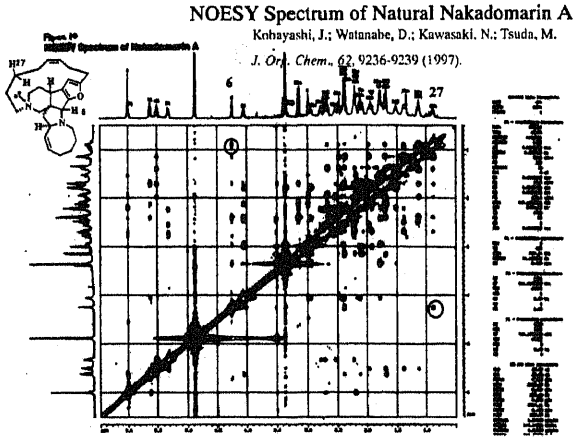


Chart 4　ﾅｶﾄﾞﾏﾘﾝA(天然由来)の差nOe



次にナカドマリンA(合成品)とナカドマリンA(天然由来)とを^{1}H NMR (MeOH-d_4)で比較した(Chart 5)。その結果、小林らのオリジナルデータ[4]と異なっていた。ナカドマリンA(合成品)の絶対構造は提唱された構造と決定されているため、詳細に小林らのオリジナルデータを比較検討した。その結果、天然由来品の方が、二つのアミノ基の近傍のプロトンが低磁場シフトしていると判明した。

Chart 5　ﾅｶﾄﾞﾏﾘﾝA(合成品)の比較

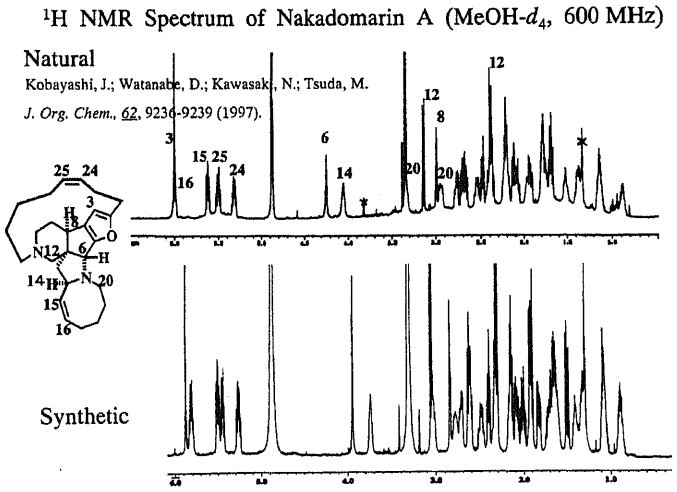
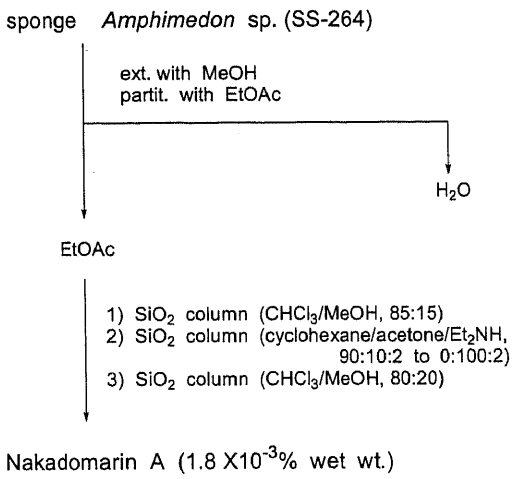


Fig. 13　ﾅｶﾄﾞﾏﾘﾝA(天然由来)の単離法[1a,c]



そこで北海道大学の小林教授らの単離精製法[1a, 1c]を調査した(Fig. 13)。その結果、海綿(*Amphimedon sp.* SS-264)からナカドマリンAを単離する際、最終の精製にシリカゲルクロマト精製(クロロホルム/メタノール, 80:20)を実施しており、クロロホルム中の微量な塩酸[6]

[3]によって塩酸塩になっていることが示唆された。

そこでナカドマリンAにDClの添加実験を行った(Chart 6)。ナカドマリンA 1当量に対してDClを0.5, 1.0, 2.0当量と徐々に増加しながら添加し、^{1}H NMRを測定した。その結果、DClの添加量の増加によって、主要なプロトンが低磁場シフトし、更にオレフィン領域も分離がよくなり、最終的に1.5から2当量のDClの添加によって報告されたスペクトルとほぼ一致した^{1}H NMRスペクトルが得られた。

Chart 6　DCl添加実験

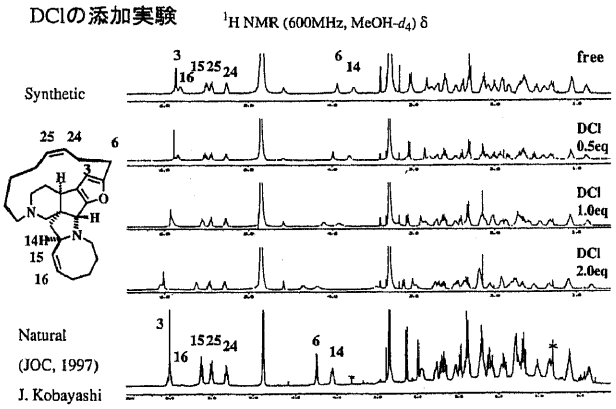
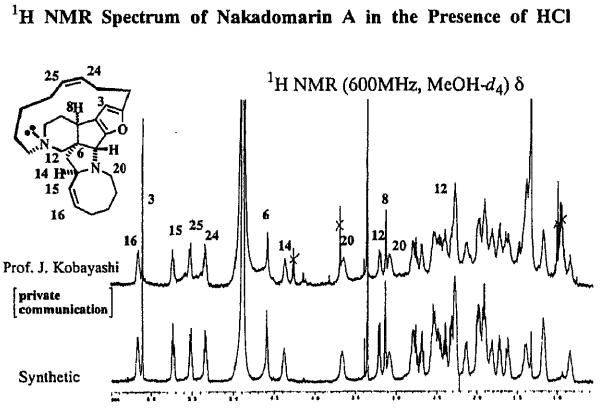


Chart 7　HCl添加実験



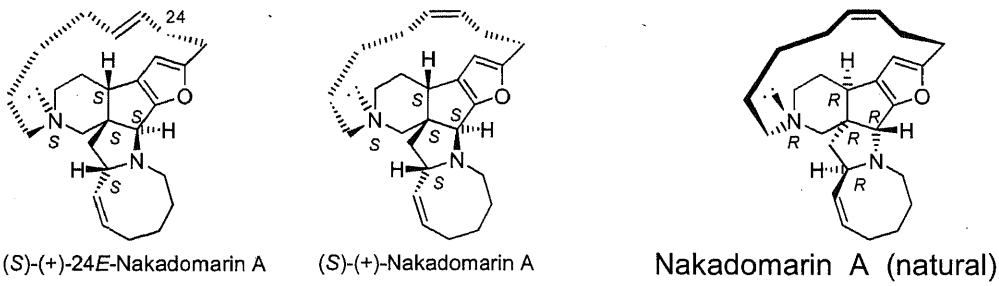
更に、北海道大学の小林 淳一 教授と津田 正史 助教授に同一条件にてHClの添加実験をしていただいた結果、ピークのよい一致を確認し、ナカドマリンA(天然由来)とナカドマリンA(合成品)の相対構造は同一と決定した(Chart 7) [64]。このようにしてナカドマリンAの不斉全合成を達成した。

次に旋光度を比較した(Table 11)。その結果、天然由来のナカドマリンAは、合成品[(*S*)-(+)-体]と逆の(*R*)-(-)-体と決定し、絶対構造を明らかにした(Fig. 14)。しかし、旋光度の絶対値に大きな差が見られた。その差は、ナカドマリンA(天然由来)の品質の問題か、一部生合成的にラセミ体を含有する可能性が示唆された。

Table 11　ナカドマリンAの旋光度

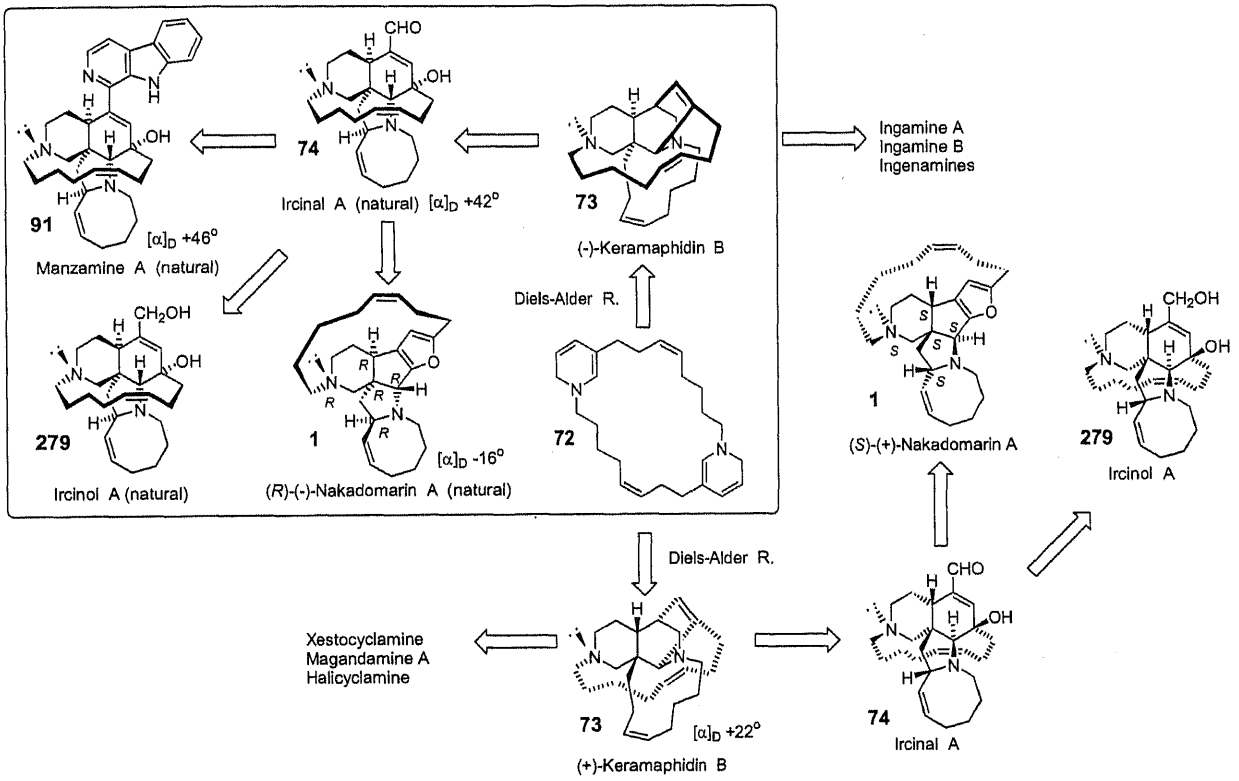
化合物名	旋光度
(*S*)-(+)-Nakadomarin A (free) (synthetic)	$[\alpha]_D^{25}$ + 70.4° (*c* 0.938, MeOH)
(*S*)-(+)-Nakadomarin A (free) (synthetic)	$[\alpha]_D^{25}$ + 79.2° (*c* 0.12, MeOH)
(*S*)-(+)-Nakadomarin A (2HCl) (synthetic)	$[\alpha]_D^{25}$ + 45.0° (*c* 0.13, MeOH)
Nakadomarin A (free? salt?) (natural)	$[\alpha]_D^{25}$ −16° (*c* 0.12, MeOH) [1a]　$[\alpha]_D$ −13° (*c* 0.12, $CHCl_3$); [1b]
(*S*)-(+)-24*E*-Nakadomarin A (free) (synthetic)	$[\alpha]_D^{25}$ + 75.2° (*c* 1.000, MeOH)

Fig. 14　ナカドマリンAの絶対構造



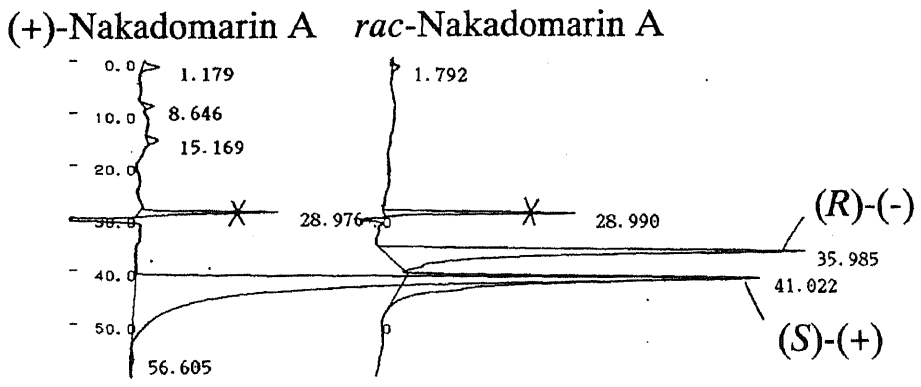
ラセミ体の含有自体は不思議ではない。小林ら自身がマンザミンアルカロイドの生合成前駆体であるKeramaphidine A (73)を単離構造決定する際、キラルHPLC分析により、ラセミ体を一部含有すると報告している(Scheme 51)[6b]。とはいえ、ナカドマリンA(天然由来)は、マイナスの旋光性を有し、絶対構造が(*R*)と決定されたため、天然由来のイルシナールA (74)より生合成されることが支持されたと考えられる。

Scheme 51　ナカドマリンAの由来について(考察)



この点を解明するためにもナカドマリンAの正確な光学純度を判定する必要があった。そこでナカドマリンAのキラルHPLC条件を探索し、下記の条件を見出した(Chart 8)。合成品の(*S*)-ナカドマリンAは、約100% eeと決定した。現在、小林教授にこのキラルHPLC条件を連絡済みであり、今後、生合成プロセスの更なる知見が得られることを期待する。

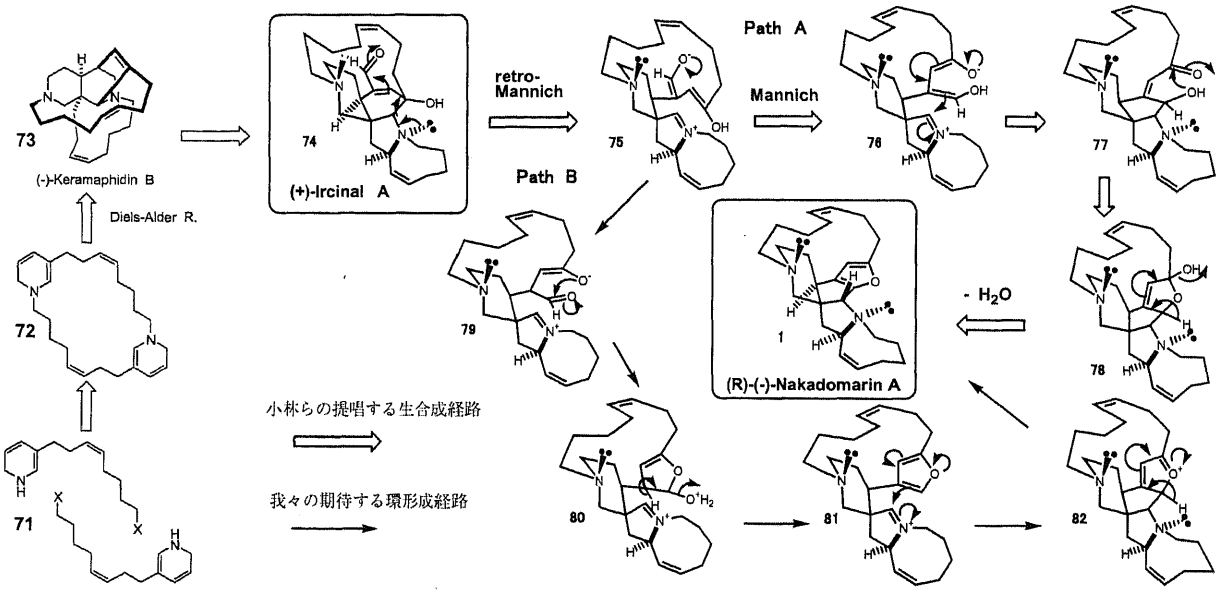
Chart 8　ナカドマリンAのキラルHPLC



CHIRALCEL OD ϕ4.6X250 mm (X3), *n*-hexane/IPA (98:2), 0.3 ml/min, 206 nm, rt.

更に、これまでの絶対配置の知見に加え、合成中間体のA環のコンホメーションの知見やF環の構造等を小林・Baldwin・Winterfeldtのナカドマリン A 1の生合成プロセス[1] に追加すると下記の経路にコンホメーションが一部修正されると考えた(Scheme 52)。

Scheme 52 ナカドマリンAの生合成経路(推定2)



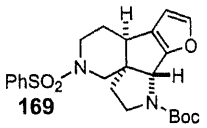
以上、筆者らは、ナカドマリンAのラセミ体の全合成、(*S*)-(+)-ナカドマリンAの不斉全合成および(*R*)-(-)-ナカドマリンAの形式不斉全合成に成功し、ナカドマリンA(天然由来)の絶対構造を(*R*)-(-)と決定した。現在、8, 14位エピマー等の合成が可能な中間体(**220**, **236**)も得られており、生合成や活性を含めた今後の展開が期待される。

以上

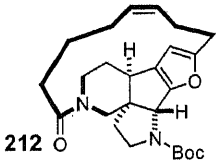
総括

筆者は、海洋産抗腫瘍活性アルカロイド ナカドマリンAの供給法の確立と絶対構造の決定を目的に全合成研究し、以下の成果を得た。

1. 分子内カチオン環化反応を鍵とし、四環性中心骨格(ABCD環)**169**の構築に成功した。更に五環性中心骨格のモデル合成**212**に成功した(第二章)。

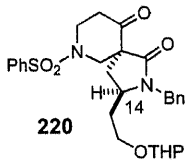


169

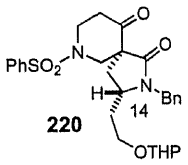


212

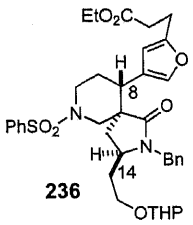
2. 他のマンザミン類や、8位,14位エピマーの合成も可能な鍵中間体(**220, 236**)を見出し、その大量合成法を確立した。この鍵中間体よりナカドマリンAのラセミ体を全合成し、5環性中間体のX線結晶構造解析と15員環のnOe実験から下記の相対構造を決定した(第三章)。



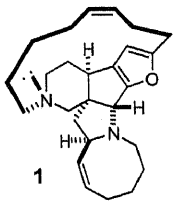
220



220

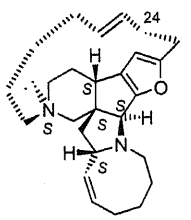


236

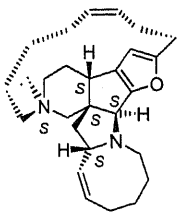


1

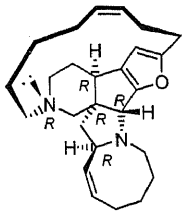
3. (*S*)-(+)-ナカドマリンAの不斉全合成および(*R*)-(-)-ナカドマリンAの形式不斉全合成に成功し、ナカドマリンA(天然由来)の絶対構造を*R*と決定した。またナカドマリンAのキラルHPLC条件を設定し、生合成経路についての知見を得る手段を与えた(第四章)。



(*S*)-(+)-24*E*-Nakadomarin A



(*S*)-(+)-Nakadomarin A



Nakadomarin A (natural)

以上

参考文献 (*References*)

1) a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* 62, 9236-9239 (1997), b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* 71, 1123-1126 (1999), c) Tsuda, M.; Watanabe, D.; Kobayashi, J. 40th Symposium on the Chemistry of Natural Products, Fukuoka, Japan, October 7-9, 1998, symposium paper pp. 467-478.

2) Magnier, E.; Langlois, Y. *Tetrahedron* 54, 6201-2258 (1998).

3) a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* 121, 11108-11113 (1999), b) Very recently Dr. Fürstner, Max-Plank-Institute, Germany, reported his synthetic approach to nakadomarin A, independently. He also showed a use of spiro-lactam a key intermediate. 18th International Congress of Heterocyclic Chemistry, Yokohama, Japan, July 29-August 3, 2001, abstracts pp.86, c) Fürstner, A.; Guth, O.; Düffels, A.; Siedel, G.; Liebl, M.; Gabor, B.; Richard, M. *Chem. Eur. J.* 7, 4811-4820 (2001), d) http://www.mpi-muelheim.mpg.de./kofo/mpikofo_home.html, e) Magnus, P.; Fielding, M.R.; Wells, C.; Lynch, V. *Tetrahedron Lett.*, 43, 947-950 (2002), f) Ono, K.; Arisawa, M.; Nakagawa, M.; Nishida, A. 122th Annual Meeting of the Pharmaceutical Society, Chiba, Japan, May 26-28, 2002, abstracts No. 2, pp. 71. g) Ono, K.; Nakagawa, M.; Nishida, A. 32nd Congress of Heterocyclic Chemistry, Tokushima, Japan, December 4-6, 2002, abstracts pp. 167.

4) Brands, K.M.J.; DiMichele, L.M. *Tetradedron Lett.* 39, 1677-1680 (1998).

5) a) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* 40, 113-166 (1999), b) Nakagawa, M.; Torisawa, Y.; Uchida, H.; Nishida, A. *J. Synth. Org. Chem., Jpn.* 57, 1004-1015 (1999).

6) a) Baldwin, J.E.; Whitehead, R.C. *Tetrahedron Lett.*, 33, 2059 (1992) b) Tsuda, M.; Inaba, K.; Kawazaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron,* 52, 2319- 2324 (1996), c) Kobayashi, J.; Tsuda, M. *J. Synth. Org. Chem., Jpn.* 55, 1114 (1 997).

7) Personal communication by Professor E. Winterfeldt.

8) a) Winkler, J.D.; Axten, J.M. *J. Am. Chem. Soc.* 120, 6425 (1998), b) Nicolaou, K.C.; Vourloumis, D.; Winssinger, N.; Baran, P.S. *Angew. Chem., Int. Ed.*, 39, 44-122 (2000).

9) a) David, M.; Dhimane, H.; Vanucci-Bacqué, C.; Lhommet, G. *Synlett* 207 (1998), b) Ohta, T.; Shiokawa, S.; Iwashita, E.; Nozoe, S. *Heterocycles* 34, 895 (1992), c) Dhimane, H.; Vanucci, C.; Lhommet, G. *Tetrahedron Lett.* 38, 1415 (1997).

10) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.*, 42, 8345-8349 (2001)

11) Fürstner, A. *Angew. Chem., Int. Ed.* 39, 3012-3043 (2000).

12) a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, Y. *Bull. Chem. Soc. Jpn.*

52, 1989-1993 (1979), b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett. 43*, 7535-7539 (2002).

13) For a recent review on intramolecular Michael reaction: Little, R.D.; Masjedizadeh, M.R.; Wallquist, O.; McLoughlin, J.I. in *Organic Reactions*; Paquette, L.A. (Ed.); Wiley: New York, 315-353 (1995).

14) Wakabayashi, T.; Saito, M. *Tetrahedron Lett. 18*, 93-96 (1977).

15) a) Shilay, V.; Alyev, A.; Grishina, G. *Bull. Soc. Chin. 101*, 751 (1992); b) Trost, B.M.; Radinov, R.; Grenzer, E.M. *J. Am. Chem. Soc. 119*, 7879 (1997); c) Hayas hi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem. 53*, 113 (1988).

16) a) Borer, B.C.; Deerenberg, S.; Bieräugel, H.; Pandit, U.K. *Tetrahedron Lett. 31*, 3191 (1994), b) Pandit, U.K.; Borer, B.C. *Pure & Appl. Chem. 68*, 659-662 (1996).

17) a) Louwrier, S.; Tuyman, A.; Hiemstra, H. *Tetrahedron 52*, 2603-2629 (1996); b) Ahman, J.; Somfai, P. *J. Chem. Soc. Parkin Trans 1* 1079 (1994).

18) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley, 312-322 (1999).

19) Hay, H.P.; Denny, W.A. *Synthetic Commun. 28*, 463 (1998).

20) Funk, R.L.; Daggett, J.U. *Heterocycles 26*, 2175 (1987).

21) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley, 503-572 (1999).

22) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley, 600-614 (1999).

23) Allylation a) Ogura, K.; Yahata, N.; Minoguchi, M.; Ohtsuki, K.; Takahashi, K.; Iida, H. *J. Org. Chem. 51*, 508 (1986), b) Ranu, B.C.; Bhar, S. *J. Chem. Soc. Parkin Trans 1* 365 (1992).

24) Appendino, G.; Cravotto, G.; Palmisano, G.; Annunziata, R. *Tetrahedron 54*, 10819 (1998).

25) a) Boer, J.J.J.; Speckamp, W.N. *Tetrahedron Lett. 16*, 4039 (1975), b) Wakabayashi, T.; Kato, Y.; Watanabe, K. *Chem. Lett.*, 1283 (1976), c) Nishiyama, T.; Woodhall, J.F.; Lawson, E.F.; Kitching, W. *J. Org. Chem. 54*, 2183 (1989)

26) a) Almedia, J.F.; Anaya, J.; Martin, N.; Grande, M.; Moran, J.R.; Caballero, M.C. *Tetrahedron Asymmetry 3*, 1431 (1992), b) Matsuki, K.; Inoue, A.; H, Ishida, Takeda, M.; Nakagawa, M.; Hino, T. *Heterocycles 36*, 937(1993)

27) a) Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc. 93*, 2897 (1971), b) Zydowsky, T.M.; Dellaria, J.F.Jr.; Nellans, H.N. *J. Org. Chem. 53*, 5607 (1988), c) Arzel, P.; Freida, V.; Weber, P.; Fadel, A. *Tetrahedron Asymmetry 10*, 3877 (1999).

28) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley,

638 (1999).

29) Kim, B.J.; Park, Y.S.; Beak, P. *J. Org. Chem. 64*, 1705 (1999).

30) Ikota, N. *Chem. Pharm. Bull., 40*, 1925 (1992)

31) Ritter, K. *Synthesis* 75 (1993).

32) a) Miyaura, N.; Suzuki, A. *Chem. Rev. 95*, 2457 (1995), b) Wustrow, D.J.; Wise, L.D. *Synthesis* 993 (1991), c) Eastwood, P.R. *Tetrahedron Lett. 41*, 3705-3708 (2000), d) Suzuki, A. *Pure Appl. Chem. 66*, 213 (1994), e) Gravett, E.C.; Hilton, P.J.; Jones, K; Romero, F. *Tetrahedron Lett. 42*, 9081 (2001), f) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc. 111*, 314-321 (1989).

33) Duan, S.Q.; Moeller, K.D. *Tetrahedron 57*, 6407 (2001)

34) Lehmann, J.; Tochtermann, W. *Tetrahedron* 55, 2639 (1999).

35) Chiarello, J.; Joullie, M.M. *Tetrahedron 44*, 41 (1988).

36) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull. 19*, 817 (1971).

37) a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem. 60*, 7508-7510 (1995), b) Murata, M.; Watanabe, S.; Masuda, S. *J. Org. Chem. 62*, 6458-6459 (1997)

38) WO/98/46265

39) a) Meyer, S.D.; Schreiber, S.L. *J. Org. Chem. 59*, 7549 (1994), b) Dess, D.B.; Martin, J.C. *J. Org. Chem. 48*, 4155 (1983).

40) Comins, D.L.; LaMunyon, D.H.; Chen, X. *J. Org. Chem. 62*, 8182 (1997).

41) Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem. 57*, 5741 (1992).

42) Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc. 118*, 100-110 (1996).

43) Scholl, M.; Ding, S.; Grubbs, R.H. *Org. Lett. 1*, 953-956 (1999).

44) Sakai, H.; Ito, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Hagiwara, H. *Tetrahedron Lett. 40*, 2965 (1999).

45) VanRheenen, G.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett. 23*, 1973 (1976).

46) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley, 207-215 (1999).

47) Jackson, D.Y. *Synthetic Commun. 18*, 337-341 (1988).

48) a) Klosterman, H.J.; Smith, F. *J. Am. Chem. Soc. 76*, 1229 (1954), b) Marx, J.N.; Norman, L.R. *J. Org. Chem. 40*, 1602 (1975).

49) Shi, Y.J.; Wells, K.M.; Pye, P.J.; Choi, W.B.; Churchill, R.O.; Lynch, J.E.; Maliakal, A.; Sager, J.W.; Rossen, K.; Volante, R.P.; Reider, P.J. *Tetrahedron 55*, 909-918 (1999)

50) Greene, T.W.; Wuts, P.G.M. *Protective Group in Organic Synthesis* 3rd. Ed.; Wiley, 49-54 (1999).

51) a) Kerwin, S.M.; Paul, A.G.; Heathcock, C.H. *J. Org. Chem., 52*, 1686 (1987), b)

Cortes, M.; Razmilic, I.; Lopez, J.; Leyton, F. *Bull. Chem. Soc. Berg.* **98**, 417 (1989), c) Lovey, R.G.; Saksena, A.K.; Girijavallabhan, V.M. *Tetrahedron Lett.* **35**, 6047 (1994).

52) Gutmann, V., "The Doner-Acceptor Approach to Molecular Interactions", JapanScientific Societies Press, Japan, 1983, pp. 32.

53) Honda, T.; Ishikawa, F. *J. Org. Chem.* **64**, 5542-5546 (1999).

54) a) Alonso, E.; Ramon, D.J.; Yus, M. *Tetrahedron* **53**, 14355-14368 (1997), b) Kok, H.-L.S.; Lee, C.C.; Shing, T.K.M. *J. Org. Chem.* **66**, 7184-7190 (2001), c) Davis, S.G.; Fenwick, D.R. *Chem. Commun.* 565 (1997), d) Groaning, M.D.; Meyers, A.I. *Chem. Commun.* 1027 (2000), e) Chemical Society of Japan, "Total Synthesis of Natural Products, Today Tomorrow and Beyond", Japan Scientific Societies Press, 2000, Kikan Kagaku Sousetsu No. 45, pp. 117.

55) Schlienger, N.; Bryce, M.R.; Hansen, T.K. *Tetrahedron* **56**, 10023-10030 (2000).

56) a) Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* **34**, 18-29 (2001), b) Grubbs, R.H.; Chang, S. *Tetrahedron* **54**, 4413-4450 (1998), c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **35**, 2037-2056 (1997), d) Fürstner, A. *Top. Catal.* **4**, 285-299 (1997), e) Armstrong, S.K. *J. Chem. Soc. Perkin Trans. 1* 371-388 (1998), f) Ivin, K.J. *J. Mol. Catal. A: Chem.* **133**, 1-16 (1998), g) Randall, M.L.; Snapper, M.L. *J. Mol. Catal. A: Chem.* **133**, 29-40 (1998), h) Schrock, R.R. *Tetrahedron* **55**, 8141-8153 (1999), i) Maier, M.E. *Angew. Chem., Int. Ed.* **39**, 2073-2077 (2000), j) Nguyen, S.T.; Johson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **114**, 3974-3975 (1992), k) Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **117**, 5503-5511 (1995), l) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem., Int. Ed.* **34**, 2039-2041 (1996), m) Schwab, P.; Grubbs R.H.; Ziller, J.W. *J. Am. Chem. Soc.* **118**, 100-110 (1996).

57) H. Uchida, Ph. D. Thesis, University of Chiba, Chiba, Japan, 2002.

58) a) Bourgeois, D.; Pancrazi, A.; Richard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **39**, 726 (2000), b) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S.P.; Prunet, J. *Synthesis* **6**, 869 (2000)

59) Humphrey, J.M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney,A.K.; Martin, S.F. *J. Am. Chem. Soc.* **124**, 8584-8592 (2002)

60) Single-crystal of olefin **262** was prepared with this condition (ca50mg/6ml MeOH). Olefin **262** was confirmed by X-ray analysis by Dr. K. Yamaguchi.

61) The solubility limits of **134** was shown. Diisopropyl ether: 0.064 w/w%. Diethyl ether: 0.28 w/w%. EtOH: 1.98 w/w%. AcOEt: 6.94w/w%.

62) Hesse, M.; Meier, H.; Zeeh, B. "Spectroscopic Methods in Organic Chemistry", 5th, Georg Thieme Verlag, Germany, 1996, pp. 121.

63) Perrin, D.D.; Armarego, W.L.F. "Purification of Labolatory Chemicals", 3rd,

Pergamon Press, Oxford, U.K., 1988, pp. 121.

Chloroform: Chloroform is unstable than dichloromethane. Reacts slowly oxygen or oxidizing agents, when exposed to air and light, giving, mainly, phosgene, Cl_2 and HCl. e.g. $CHCl_3 + 1/2O_2 \rightarrow COCl_2 + HCl$; $2CHCl_3 + 5/2O_2 \rightarrow 2CO_2 + 3Cl_2 + H_2O$. Commercial $CHCl_3$ was stabilized by addn of up to 1% EtOH or of dimethylaminoazobenzene.

64) Personal communication by Professors J. Kobayashi and M. Tsuda. The natural nakadomarin A, which was treated with alumina, was observed upfileded shifts.

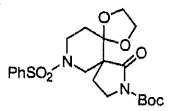
実験の部 (Experimental Section)

1,2-Dimethoxyethane (DME) was distilled from sodium/benzophenone prior to use. Another anhydrous solvents [*N,N*-dimethylformamide (DMF), ethanol (EtOH), methanol (MeOH), tetrahydrofuran (THF) and toluene] were used as received from Wako Pure Chemical Industries, Ltd. All commercially available compounds (Wako, TCI, Aldrich and Lancaster) were used as received.

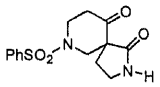
General: All reactions were carried under an argon atmosphere. Melting points were recorded on a Yamato MP-21 melting point apparatus, and are uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H NMR spectra were taken on 200-500 MHz instruments (Bruker DPX-300, JEOL JMN-GSX 500, JEOL JMN-ECP 600) in the indicated solvent at rt unless otherwise stated and are reported as follows: chemical shifts [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened), coupling constants in hertz, integration]. ^{13}C NMR were taken at 75-150 MHz in the indicated solvent and are reported as follows: chemical shift (multiplicity detected by DEPT). HPLC analyses were performed on Hitachi 655 liquid chromatograph, Hitachi 638-41 variable wavelength UV monitor (detected at 254 nm or 206 nm), Hitachi D-2500 chromato-integrator, and Daicel chiral column (Chiralcel OD or Chiralpak AD, Daicel Chemical Ind., Ltd.). Analytical TLC was carried on Merck DC-Platten Kieselgel 60 GF_{254} plates, and on Merck DC-Fertigplatten Aluminiumoxid 60 F_{254} (Type E) plate. Preparative TLC was carried on Merck Kieselgel 60 GF_{254} plates. Silica gel column chromatography was performed using Silica gel BW-820 (Fuji Silysia Chemical Ltd.). Alumina column chromatography was performed using Merck Aluminiumoxid 90 aktivbasisch. Elemental analyses and MS spectrometry were carried out by Takeda Analytical Research Laboratories, Ltd. and Chemical Analysis Center of Chiba University. X-ray crystallographic analyses were performed by Dr. K. Yamaguchi at The Chemical Analysis Center of Chiba University.

8-(*t*-Butoxycarbonyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecan e-7-one (119). To a solution of amide **126** (60 mg, 0.17 mmol), DMAP (1 mg, 0.009 mmol) and Et_3N (0.03 mL, 0.20 mmol) in THF (0.6 mL) was added di-*tert*-butyldicarbonate (46 mg, 0.20 mmol) at rt. After stirring for 17 h at rt, the reaction mixture was concentrated in vacuo and extracted with EtOAc, washed with 1 *N* HCl aqueous solution, sat. $NaHCO_3$ aqueous solution and brine successively. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 50% EtOAc in *n*-hexane) to afford **119** (76 mg, 99%): R_f = 0.20 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.71

(ddd, J = 13.41, 6.33, 3.15 Hz, 1H), 2.01 (ddd, J = 17.04, 13.41, 5.25 Hz, 1H), 2.14-2.24 (m, 1H), 2.27-2.36 (m, 1H), 2.72 (ddd, J = 11.74, 5.25, 3.15 Hz, 1H), 3.05 (d, J = 11.72 Hz, 1H), 3.50 (dd, J = 11.72, 2.02 Hz, 1H), 3.65-3.93 (m, 3H), 3.94-4.04 (m, 4H), 7.49-7.63 (m, 3H), 7.72 (dd, J = 8.52, 1.49 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 28.4, 32.7, 43.7, 44.7, 51.7, 53.3, 65.8, 65.9, 83.4, 109.4, 127.8, 129.6, 133.4, 136.8, 150.3, 172.0; IR (thin film) 1778, 1747, 1716, 1369 cm^{-1}.

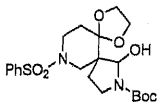


7-(Phenylsulfonyl)-2,7-diazaspiro[4.5]decane-1,10-dione (127). To a solution of ketal **126** (2.15 g, 6.10 mmol) in CH_2Cl_2 (75 mL) was added 70% aqueous perchloric acid (11 mL) at rt. After stirring slowly for 2.5 h, the reaction mixture was carefully pored into aq. sat. $NaHCO_3$ solution. Separated aqueous layers were extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc/diisopropyl ether to give **127** as a colorless crystal (1.61 g, 85%): R_f = 0.03 (silica gel, EtOAc/*n*-hexane, 1:2); mp 177.0-179.0 °C dec. (EtOAc/ *n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (ddd, J = 13.57, 7.55, 3.90 Hz, 1H), 2.47-2.55 (ddd, J = 15.83, 13.57, 7.63 Hz, 1H), 2.61-2.69 (ddd, J = 15.78, 9.32, 4.72 Hz, 1H), 2.73-2.83 (ddd, J = 15.78, 9.61, 6.36 Hz, 1H), 3.05 (dddd, J = 14.51, 9.61, 4.72 Hz, 1H), 3.31-3.42 (m, 2H), 3.35 (d, J = 12.31 Hz, 1H), 3.47 (dd, J = 12.31, 1.24 Hz, 1H), 3.77-3.85 (m, 1H), 6.72 (brs, 1H), 7.52-7.65 (m, 3H), 7.78 (dd, J = 8.72, 1.62 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 38.3, 39.4, 45.9, 52.9, 58.5, 127.9, 129.8, 133.7, 136.6, 174.0, 204.0; IR (KBr) 3300, 1720, 1697, 1362 cm^{-1}; LRMS 309 (FAB, M + H); HRMS Calculated for $C_{14}H_{17}N_2O_4S$ 309.0909 (FAB, M + H). Found 309.0904 (FAB, M + H); Anal. Calculated for $C_{14}H_{16}N_2O_4S$ C: 54.53, H: 5.23, N: 9.08, O: 20.75, S: 10.40. Found C: 54.47, H: 4.95, N: 9.13.

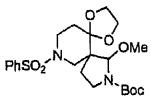


8-(*t*-Butoxycarbonyl)-7-hydroxy-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane (120). To a solution of carbamate **119** (70 mg, 0.15 mmol) in toluene (1 mL) and CH_2Cl_2 (1 mL) was added dropwise a 1.5 M solution of DIBAL-H in toluene (0.40 mL, 0.27 mmol) at −78 °C. After stirring for 1 h, the reaction mixture was warmed to 0 °C over 1 h and stirring was continued for 1 h at rt. After the solution was cooled to −78 °C, 0.7 M Rochelle's salt (1 mL) was added dropwise and then the mixture was warmed to 0 °C over 1 h and stirred for 1 h at rt. After EtOAc (400 mL) and 0.7 M Rochelle's salt (150 mL) were added, separated organic layer was washed with 0.7 M Rochelle's salt (150 mL, three times) and brine (220 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 50% to 70% EtOAc in *n*-hexane) to afford **120** as a colorless syrup (59 mg, 84%): ^{1}H NMR (300

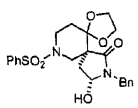
MHz, $CDCl_3$) δ 1.49 (s, 45/11H), 1.52 (s, 54/11H), 1.65-1.90 (m, 22/11H), 1.85-2.05 (m, 11/11H), 2.05-2.30 (m, 11/11H), 2.69 (d, J = 11.17 Hz, 6/11H), 2.80 (d, J = 11.39 Hz, 5/11H), 2.82-3.00 (brm, 11/11H), 3.12 (d, J = 11.39 Hz, 5/11H), 3.19 (d, J = 11.17 Hz, 6/11H), 3.34-3.58 (m, 33/11H), 3.75-4.05 (m, 55/11H), 5.23 (brs, 5/11H), 5.43 (brd, J = 4.69 Hz, 6/11H), 7.48-7.63 (m, 3H), 7.72 (d, J = 7.01 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 26.1, 28.8, 32.4, 32.6, 42.4, 43.1, 44.6, 50.3, 50.8, 52.0, 54.2, 64.2, 64.5, 65.9, 66.3, 80.9, 84.3, 84.8, 108.9, 127.8, 129.6, 133.3, 137.2, 154.8, 155.1; IR (thin film) 1693, 1360 cm^{-1}; LRMS (FAB, M + K – C_2H_4O): 449; HRMS Calculated for $C_{19}H_{26}N_2O_6SK$ (FAB, M + K – C_2H_4O): 449.1149. Found 449.1197.



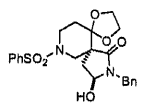
8-(*t*-Butoxycarbonyl)-7-methoxy-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane (122). To a solution of aminal **120** (27 mg, 0.06 mmol) and orthoformic acid trimethyl ether (32mg, 0.30 mmol) in methanol (0.7 mL) was added PPTS (2.2 mg, 9.0 μmol) at rt. After stirring for 2 h, the reaction was quenched by addition of sat. $NaHCO_3$ aqueous solution and extracted with EtOAc. Combined organic layers were washed with water, dried over $MgSO_4$, and concentrated in vacuo affording **122** as a syrup (25 mg, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 99/11H), 1.20-2.20 (m, 44/11H), 2.50-2.85 (m, 22/11H), 3.31 (s, 33/11H), 3.31-3.74 (m, 44/11H), 3.75-4.10 (m, 44/11H), 4.98 (s, 4/11H), 5.10 (s, 7/11H), 7.49-7.59 (m, 33/11H), 7.75 (m, 22/11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 28.9, 30.1, 30.2, 31.4, 31.6, 44.7, 44.9, 45.5, 50.6, 50.9, 54.2, 55.0, 56.3, 56.4, 65.2, 65.3, 79.9, 80.2, 89.7, 90.1, 109.5, 127.9, 129.5, 129.5, 133.0, 137.1, 154.5, 155.7; IR (thin film) 1695, 1338 cm^{-1}.



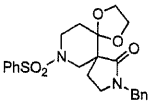
8-Benzyl-9-hydroxy-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one (139). To a solution of **134** (974 mg, 2.13 mmol) and MC-OsO_4 (309 mg, 0.22 mmol) in THF/water (5:1, 60 mL) was added $NaIO_4$ (1.37 g) at rt. After stirring for 15 h, the reaction was quenched by addition of 5 *N* $Na_2S_2O_4$ (100 mL) aqueous solution. The solid material was filtered off and washed with EtOAc. The filtrate was extracted with EtOAc (600 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 41% to 55% EtOAc in *n*-hexane) to afford acetate **139** as a colorless syrup (643 mg, 66%): **(6*S**, 9*R**)-8-Benzyl-9-hydroxy-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*S**, 9*R**)-139] (More Polar, H-14β)**: R_f = 0.23 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.66-1.72 (m, 1H), 2.03-2.12 (m, 1H), 2.16 (dd, J = 15.17, 0.00 Hz, 1H), 2.45 (dd, J = 15.17, 6.86 Hz, 1H), 2.60-2.69 (m, 1H), 3.10 (d, J = 11.77 Hz, 1H), 3.48 (dd, J = 11.77, 2.29 Hz, 1H),



3.70-3.95 (m, 6H), 4.22 (d, J = 14.55 Hz, 1H), 4.79 (d, J = 14.55 Hz, 1H), 4.89 (dd, J = 12.35, 6.71 Hz, 1H), 7.26-7.36 (m, 5H), 7.48-7.62 (m, 3H), 7.72-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 39.2, 44.2, 44.4, 50.6, 52.8, 65.1, 65.5, 79.6, 108.5, 127.4, 127.7, 128.6, 129.3, 133.0, 136.2, 136.2, 171.0; IR (thin film) 3450, 2966, 2898, 2868, 1693, 1446, 1358, 1336, 1261, 1225, 1169, 1090, 1030, 970, 951, 912, 735, 704, 692, 594, 579 cm^{-1}; LRMS 459 (FAB, M + H); HRMS Calculated for $C_{23}H_{27}N_2O_6S$ 459.1590 (FAB, M + H). Found 459.1625. **(6*S***, 9*S**)-8-Benzyl-9-hydroxy-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*S**, 9*S**)-139] (Less Polar, H-14α)**: R_f = 0.30 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-1.75 (m, 1H), 1.88-1.99 (m, 1H), 1.98-2.04 (dd, J = 14.20, 3.66 Hz, 1H), 2.44 (brd, J = 7.92 Hz, 1H), 2.63 (dd, J = 14.20, 6.70 Hz, 1H), 2.70-2.79 (m, 1H), 3.19 (d, J = 11.70 Hz, 1H), 3.54-3.61 (m, 2H), 3.68-3.72 (m, 1H), 3.70-3.78 (m, 1H), 3.82-3.90 (m, 2H), 4.20 (d, J = 14.81 Hz, 1H), 4.86 (d, J = 14.81 Hz, 1H), 5.08-5.14 (m, 1H), 7.26-7.34 (m, 5H), 7.49-7.62 (m, 3H), 7.73-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 32.7, 38.6, 43.5, 44.3, 51.7, 52.2, 65.0, 65.7, 80.0, 108.8, 127.5, 127.6, 128.3, 128.7, 129.2, 132.9, 136.2, 136.6, 171.3; IR (thin film) 3250, 2954, 2924, 2854, 1668, 1466, 1336, 1358, 1336, 1169, 1095, 1030, 968, 908, 742, 692, 578 cm^{-1}; LRMS (FAB, M + H): 459; HRMS Calculated for $C_{23}H_{27}N_2O_6S$ (FAB, M + H): 459.1590. Found 459.1630.

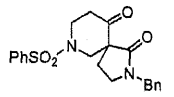


8-Benzyl-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one (123). To a solution of **139** (200 mg, 0.44 mmol) in TFA (0.34 mL) was added triethylsilane (0.08 mL, 0.52 mmol) at rt. After stirring for 0.5 h, the reaction mixture was extracted with EtOAc. Combined organic layers were washed with water, aq. sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 41% to 50% EtOAc in *n*-hexane) to afford acetate **123** as a colorless solid (105 mg, 60%): R_f = 0.29 (silica gel, EtOAc/*n*-hexane, 2:1); mp 159.0-160.0 °C (AcOEt/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (ddd, J = 16.82, 6.18, 3.10 Hz, 1H), 2.02 (ddd, J = 16.82, 12.04, 4.90 Hz, 1H), 2.18 (ddd, J = 13.50, 9.10, 7.35 Hz, 1H), 2.29 (ddd, J = 13.50, 8.33, 3.76 Hz, 1H), 2.72 (ddd, J = 14.77, 12.04, 3.10 Hz, 1H), 3.09 (d, J = 11.65, 2.00 Hz, 1H), 3.17 (ddd, J = 15.29, 9.10, 3.76 Hz, 1H), 3.32 (dd, J = 15.29, 8.33, 7.35 Hz, 1H), 3.46 (dd, J = 11.65, 2.00 Hz, 1H), 3.64-3.74 (m, 1H), 3.78-3.98 (m, 4H), 4.32 (d, J = 14.65 Hz, 1H), 4.58 (d, J = 14.65 Hz, 1H), 7.21 (m, 5H), 7.50 (m, 3H), 7.75 (dd, J = 8.73, 1.52 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 33.1, 44.3, 44.8, 47.4, 51.9, 52.3, 65.5, 65.9, 109.8, 127.9, 128.0, 128.5, 129.1, 129.6, 133.3, 136.6, 136.9, 172.2; IR (KBr) 1685 cm^{-1}; Anal.

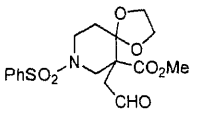


Calculated for $C_{23}H_{26}N_2O_5S$ C: 62.42, H: 5.92, N: 6.33, O: 18.08, S: 7.25. Found C: 62.22, H: 5.95,N: 6.13.

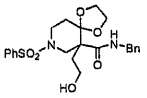
2-Benzyl-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-1,10-dione (128). To a solution of ketal **123** (2.50 g, 5.91 mmol) in CH_2Cl_2 (17.5 mL) was added 70% aqueous perchloric acid (2.4 mL) at rt. After stirring slowly for 1 h, the reaction mixture was carefully pored into aq. sat. $NaHCO_3$ solution. Separated aqueous layers were extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc/diisopropyl ether to give **128** as a colorless crystal (1.59 g, 71%): R_f = 0.25 (silica gel, EtOAc/*n*-hexane, 1:1); mp 138.0-139.0 °C (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15-2.30 (m, 1H), 2.35-2.50 (m, 1H), 2.65-2.75 (m, 1H), 2.75-2.90 (m, 1H), 2.95-3.15 (m, 1H), 3.25 (dd, J = 8.23, 5.54 Hz, 2H), 3.45 (d, J = 12.31 Hz, 1H), 3.73 (dd, J = 12.31, 2.38 Hz, 1H), 3.80-3.95 (m, 1H), 4.49 (d, J = 14.91 Hz, 1H), 4.57 (d, J = 14.91 Hz, 1H), 7.20-7.45 (m, 5H), 7.65-7.75(m, 3H), 7.82 (dd, J = 8.61, 1.53 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0, 38.1, 43.8, 45.8, 47.4, 53.3, 59.5, 127.9, 128.2, 128.4, 129.2, 129.8, 133.7, 136.0, 136.7, 170.6, 204.1; IR (KBr) 1712, 1691, 1679, 1358 cm^{-1}; Anal. Calculated for $C_{21}H_{22}N_2O_4S$ C: 63.30, H: 5.56, N: 7.03, O: 16.06, S: 8.05. Found C: 63.12, H: 5.56, N: 6.83.



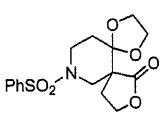
Methyl 6-(2-Oxoethyl)-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (142). To a solution of **132** (1.0 g, 2.62 mmol) and MC-OsO_4 (380 mg, 0.15 mmol) in THF/water (4:1, 50 mL) was added $NaIO_4$ (1.68 g) at rt. After stirring for 4 h, the reaction was quenched by addition of 5 *N* $Na_2S_2O_4$ (5 mL) aqueous solution. The residue was filtered off and washed with EtOAc. The filtrate was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 41% EtOAc in *n*-hexane) to afford aldehyde **142** as a colorless solid (533 mg, 53%): R_f = 0.65 (silica gel, EtOAc); mp 174.0-175.5 °C dec. (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (ddd, J = 13.89, 7.47, 3.64 Hz, 1H), 1.92 (ddd, J = 13.89, 11.33, 4.98 Hz, 1H), 2.73 (ddd, J = 15.00, 11.33, 3.64 Hz, 1H), 3.11 (d, J = 18.38 Hz, 1H), 3.18 (d, J = 12.73 Hz, 1H), 3.24 (d, J = 18.38 Hz, 1H), 3.72-3.95 (m,6H), 3.70 (s, 3H), 7.50-7.63 (m, 3H), 7.76 (dd, J = 6.88, 1.59 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 44.6, 44.8, 49.3, 51.7, 52.8, 65.5, 65.6, 108.4, 127.8, 129.6, 133.3, 137.3, 171.3, 198.9; IR (KBr) 1743, 1725 cm^{-1}; Anal. Calculated for $C_{17}H_{21}NO_7S$ C: 53.25, H: 5.52, N: 3.65, O: 29.21, S: 8.36. Found C: 53.07, H: 5.51, N: 3.63; LRMS 384 (FAB, M + H).



N-Benzyl-1,4-dioxa-6-(2-hydroxyethyl)-8-(phenylsulfonyl)-8-azaspiro[4.5]decane-6-carboxamide (138). To a solution of aldehyde **135** (500 mg, 1.09 mmol) in THF/EtOH (5:2, 14 mL) was added $NaBH_4$ (12 mg, 0.30 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched by addition of water and concentrated in vacuo. The residue was dissolved in EtOAc and the solution was washed with 1 *N* HCl and water, dried over $MgSO_4$, and concentrated in vacuo. To a solution of the residue in THF (5 mL) were added 3 *N* NaOH (0.5 mL) aqueous solution and 30% aqueous H_2O_2 (0.2 mL) at 0 °C. After stirring for 1 h, the mixture was quenched by addition of 5 *N* $Na_2S_2O_4$ (1 mL) aqueous solution, extracted with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue (552 mg) was recrystallized from EtOAc/diisopropyl ether to give **138** as a colorless crystal (260 mg, 52%): R_f = 0.06 (silica gel, EtOAc/*n*-hexane, 1:1); mp 166 °C dec. (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (ddd, J = 13.68, 7.41, 3.63 Hz, 1H), 1.88-1.96 (m, 1H), 1.98-2.08 (m, 1H), 2.21-2.28 (m, 1H), 2.65-2.69 (m, 1H), 3.12 (d, J = 12.80 Hz, 1H), 3.50-4.00 (m, 8H), 4.22 (dd, J = 14.45, 9.78 Hz, 1H), 4.65 (dd, J = 14.45, 7.02 Hz, 1H), 6.95 (brs, 1H), 7.26-7.33 (m, 5H), 7.51-7.61 (m, 3H), 7.80 (dd, J = 7.94, 1.04 Hz, 2H); IR (KBr) 3343, 1643, 1351 cm^{-1}.

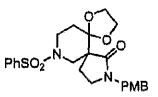


12-(Phenylsulfonyl)-1,4,8-trioxa-12-azaspiro[4.0.4.4]tetradecan-7-one (143). To a suspension of aldehyde **142** (5.0 g, 13.05 mmol) in MeOH (20 mL) was added $NaBH_4$ (136 mg, 3.60 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched by addition of 1 *N* HCl (3.6 mL) aqueous solution and concentrated in vacuo. The residue was dissolved in EtOAc, and the solution was washed with 1 *N* HCl and water, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from EtOAc/diisopropyl ether to give **143** as a colorless crystal (3.31 g, 72%): R_f = 0.23 (silica gel, EtOAc/*n*-hexane, 1:1); mp 134.0-135.0 °C (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (ddd, J = 13.44, 6.25, 3.15 Hz, 1H), 2.04 (ddd, J = 13.44, 11.96, 4.97 Hz, 1H), 2.40-2.60 (m, 2H), 2.70 (ddd, J = 14.96, 11.96, 3.15 Hz, 1H), 3.02 (d, J = 11.77 Hz, 1H), 3.54 (dd, J = 11.77, 2.19 Hz, 1H), 3.71-3.79 (m, 1H), 3.85-3.98 (m, 4H), 4.28-4.44 (m, 2H), 7.50-7.64 (m, 3H), 7.74 (dd, J = 8.43, 1.53 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8, 32.8, 44.7, 50.7, 51.7, 65.8, 66.1, 66.3, 109.1, 127.8, 129.7, 133.5, 136.8, 175.5; IR (KBr) 1765 cm^{-1}.

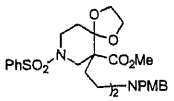


8-(4-Methoxybenzyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one (144) and Methyl

6-[2-[*N*,*N*-Bis(4-methoxybenzyl)amino]ethyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (145). To a solution of aldehyde **142** (10.0 g, 26.10 mmol) and *p*-methoxybenzylamine (11.82 g, 86.13 mmol) in MeOH (100 mL) was added AcOH (1.57 g, 26.10 mmol) at rt. After stirring for 0.5 h, $NaBH_3CN$ (1.97 g, 31.35 mmol) was added to the mixture. The mixture was stirred at 80 °C for 4 h and then cooled to rt. The reaction was quenched by addition of water, and the mixture was concentrated in vacuo. The residue was dissolved in EtOAc and the solution was washed with water, 1 *N* HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 53% EtOAc in *n*-hexane) to afford aldehyde **144** as a colorless amorphous solid (9.47 g, 77%): **8-(4-Methoxybenzyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one (144)**: R_f = 0.38 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (ddd, J = 15.00, 6.36, 3.07 Hz, 1H), 1.92 (ddd, J = 15.00, 11.65, 4.78 Hz, 1H), 2.05 (dddd, J = 13.39, 8.58, 6.43, 1.85 Hz, 1H), 2.20 (ddd, J = 13.39, 8.58, 3.71 Hz, 1H), 2.68 (ddd, J = 14.54, 11.65, 3.07 Hz, 1H), 3.03 (d, J = 11.70 Hz, 1H), 3.01-3.10 (m, 1H), 3.22 (dd, J = 16.17, 8.58 Hz, 1H), 3.34 (dd, J = 11.70, 1.62 Hz, 1H), 3.57-3.66 (m, 2H), 3.71 (s, 3H), 3.71-3.90 (m, 3H), 4.15 (d, J = 14.48 Hz, 1H), 4.43 (d, J = 14.48 Hz, 1H), 6.78 (d, J = 8.59 Hz, 2H), 7.08 (d, J = 8.59 Hz, 1H), 7.41-7.54 (m, 3H), 7.67 (dd, J = 8.62, 1.53 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 32.9, 44.1, 44.8, 46.6, 51.9, 52.3, 55.6, 65.5, 65.9, 109.7, 114.4, 127.8, 128.7, 129.6, 129.8, 133.3, 136.8, 159.5, 172.0; IR (KBr) 1685, 1355 cm^{-1}; LRMS 473 (FAB, M + H); HRMS Calculated for $C_{24}H_{29}N_2O_6S$ 473.1746 (FAB, M + H). Found 473.1721.

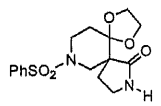


Methyl 6-[2-[*N*,*N*-Bis(4-methoxybenzyl)amino]ethyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (145): R_f = 0.26 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.67-2.01 (m, 2H), 1.90-2.10 (m, 2H), 2.10-2.40 (m, 4H), 2.45-2.75(m, 4H), 2.85-3.00 (m, 2H), 3.35-3.70 (m, 11H), 3.70-3.95 (m, 12H), 6.82-6.87 (m, 2H), 7.25 (m, 2H), 7.49-7.61 (m, 6H), 7.52-7.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.4, 31.9, 32.1, 44.9, 48.1, 48.6, 49.1, 49.2, 52.28, 52.30, 53.8, 53.9, 55.7, 57.9, 58.4, 60.8, 65.2, 65.3, 65.4, 65.7, 109.2, 109.3, 113.81, 113.84, 127.76, 127.81, 127.9, 128.05, 128.08, 129.49, 129.58, 129.61, 129.7, 129.8, 130.5, 130.7, 132.0, 132.2, 133.1, 136.6, 136.7, 158.80, 158.84, 172.4, 172.6; IR (KBr) 1766, 1736, 1360 cm^{-1}; LRMS 872 (FAB, M + H); HRMS Calculated for $C_{42}H_{54}N_3O_{13}S$ 872.3098 (FAB, M + H). Found 872.3069 (FAB, M + H).

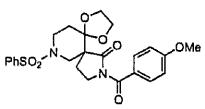


12-(Phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecan-7-one and **8-(4-Methoxybenzoyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradeca**

ne-7-one (126). To a solution of **144** (4.27 g, 9.04 mmol) in MeCN/water (30 mL/12.8 mL) was added CAN (14.86 g, 27.11 mmol) at rt. After stirring for 10 min, the residue was extracted with CH_2Cl_2 (300 mL, three times) and the solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 100% EtOAc in *n*-hexane) to afford lactam **126** (2.18 g, 69%) and imide **150** (0.76 g, 17%): **12-(Phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecan-7-one (126)**: R_f = 0.05 (silica gel, EtOAc/*n*-hexane, 2:1); mp 208.0-209.0 °C (EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (ddd, J = 12.23, 6.31, 3.11 Hz, 1H), 2.01 (ddd, J = 14.85, 12.23, 4.88 Hz, 1H), 2.24-2.45 (m, 2H), 2.70 (ddd, J = 14.85, 11.81, 3.11 Hz, 1H), 2.99 (d, J = 11.64 Hz, 1H), 3.25-3.42 (m, 2H), 3.47 (dd, J = 11.64, 2.10 Hz, 1H), 3.68-3.74 (m, 1H), 3.83-4.02 (m, 4H), 6.45 (brs, 1H), 7.26-7.59 (m, 3H), 7.73 (dd, J = 8.46, 1.13 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 33.0, 39.4, 44.8, 50.7, 65.8, 65.9, 109.6, 127.9, 129.6, 133.3, 136.8, 176.2, ; IR (KBr) 3250, 1697, 1356 cm^{-1}; LRMS 353 (FAB, M + H); HRMS Calcd for $C_{16}H_{21}N_2O_5S$ 353.1171 (FAB, M + H). Found 353.1213.

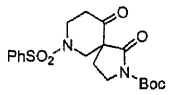


8-(4-Methoxybenzoyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradeca ne-7-one (150): R_f = 0.49 (silica gel, EtOAc/*n*-hexane, 2:1); mp 197.5-198.5 °C (EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (t, J = 6.65 Hz, 2H), 2.12-2.24 (m, 1H), 2.37-2.46 (m, 1H), 2.89-2.98 (m, 1H), 3.25 (d, J = 11.74 Hz, 1H), 3.38 (d, J = 11.74 Hz, 1H), 3.45-3.51 (m, 1H), 3.79-4.01 (m, 6H), 3.84 (s, 3H), 6.89 (d, J = 8.83 Hz, 2H), 7.49-7.67 (m, 3H), 7.60 (d, J = 8.83 Hz, 2H), 7.75 (dd, J = 8.54 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 32.1, 43.4, 44.6, 51.5, 53.9, 55.8, 65.6, 65.9, 109.2, 113.6, 126.6, 127.8, 129.6, 131.9, 133.3, 137.0, 163.3, 170.2, 172.6; IR (thin film) 1739, 1670, 1360 cm^{-1}; Anal. Calculated for $C_{24}H_{26}N_2O_7S$ C: 59.25, H: 5.39, N: 5.76,O: 23.02, S: 6.59. Found C: 59.04, H: 5.48, N: 5.58.

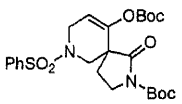


***tert*-Butyl 1,10-Dioxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (151) and *tert*-Butyl 1-Oxo-7-(phenylsulfonyl)-10-[(*tert*-butyloxycarbonyl)oxy]-2,7-diazaspiro[4.5]dec-9-ene-2 -carboxylate (152).** To a solution of amide **127** (1.52 g, 3.44 mmol), DMAP (30 mg, 0.25 mmol) and Et_3N (550 mg, 5.44 mmol) in THF (50 mL) was added di-*tert*-butyldicarbonate (1.06 g, 3.44 mmol) at 0 °C. After stirring for 1.5 h at rt, the reaction was quenched by water and extracted with EtOAc. Combined organic layers were washed with 0.5 *N*HCl aqueous solution, sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column

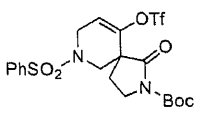
chromatography (silica gel, 10% to 90% EtOAc in *n*-hexane) to afford **151** (1.24 g, 62%) and Boc enolate **152** (114 mg, 5%). ***tert*-Butyl 1,10-Dioxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (151)**: R_f = 0.59 (silica gel, EtOAc/*n*-hexane, 2:1); mp 156.0-157.0 °C dec. (EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 2.13-2.24 (m, 1H), 2.39-2.48 (m, 1H), 2.64 (ddd, J = 15.75, 8.87, 4.55 Hz, 1H), 2.80 (ddd, J = 15.75, 9.87, 6.52 Hz, 1H), 3.02 (ddd, J = 14.60, 9.87, 4.55 Hz, 1H), 3.39 (d, J = 12.40 Hz, 1H), 3.59-3.68 (m, 1H), 3.69 (dd, J = 12.40, 2.37 Hz, 1H), 3.76-3.91 (m, 2H), 7.67-7.67 (m, 3H), 7.78 (dd, J = 7.07, 1.49 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 28.8, 37.9, 43.6, 45.8, 53.0, 61.0, 84.1, 127.9, 129.8, 133.8, 136.6, 149.9, 169.9, 203.0; IR (thin film) 1782, 1751, 1716, 1369 cm^{-1}; Anal. Calculated for $C_{19}H_{24}N_2O_6S$ C: 55.87, H: 5.92, N: 6.86, O: 23.50, S: 7.85. Found C: 55.89, H: 5.77, N: 6.90; LRMS 409 (FAB, M + H).



***tert*-Butyl 1-Oxo-7-(phenylsulfonyl)-10-[(*tert*-butyloxycarbonyl)oxy]-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (152)**: R_f = 0.72 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9H), 1.57 (s, 9H), 2.29-2.36 (m, 2H), 2.81 (d, J = 15.91 Hz, 2H), 3.29 (dd, J = 15.91, 2.13 Hz, 1H), 3.70-3.84 (m, 3H), 4.15 (dd, J = 15.88, 4.96 Hz, 1H), 5.83 (dd, J = 4.96, 2.12 Hz, 1H), 7.52-7.66 (m, 3H), 7.76 (dd, J = 8.62, 1.49 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 28.0, 28.4, 43.6, 44.2, 50.4, 52.3, 83.9, 84.2, 112.1, 127.9, 129.7, 133.7, 136.1, 145.6, 150.2, 151.0, 171.2; IR (thin film) 1782, 1761, 1720, 1369 cm^{-1}; LRMS 531(FAB, M + Na); HRMS Calculated for $C_{24}H_{32}N_2O_8SNa$ 531.1777 (FAB, M + Na). Found 531.1801.

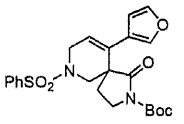


***tert*-Butyl 1-Oxo-7-(phenylsulfonyl)-10-[[(trifluoromethyl)sulfonyl]oxy]-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (153)**. A 1.0 M solution of lithium bis(trimethylsilyl)amide (0.87 mL, 0.87 mmol) in THF was added dropwise to a solution of **151** (300 mg, 0.73 mmol) in THF (2 mL) at –78 °C for 20 min. The resulting solution was stirred for 45 min at the same temperature before *N*-phenylbis(trifluoromethanesulfonimide) (297 mg, 0.83 mmol) in THF (4 mL) was introduced. Stirring was continued for additional 3 h at ambient temperature. The reaction was quenched by addition of CH_2Cl_2 (7 mL). The mixture was filtered through a pad of alumina. The pad was washed with CH_2Cl_2, and combined filtrate were concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 50% EtOAc in *n*-hexane) to afford **153** as a colorless foam (190 mg, 50%): R_f= 0.37 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (s, 9H), 2.38-2.45 (m, 2H), 2.87 (d, J = 11.71 Hz, 1H), 3.35 (dd, J = 16.26, 2.15 Hz, 1H), 3.76-3.91 (m, 2H), 3.86 (dd, J =



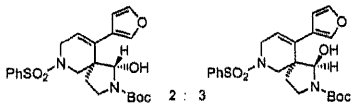
11.71, 0.95 Hz, 1H), 4.24 (ddd, J = 16.26, 5.03, 0.95 Hz, 1H), 5.99 (dd, J = 5.03, 2.15 Hz, 1H), 7.44-7.71 (m, 3H), 7.78 (dd, J = 8.76, 1.53 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 28.3, 43.4, 44.3, 50.8, 52.7, 84.5, 115.4, 118.6 (q, $^1J_{CF}$ = 320.11 Hz), 127.9, 129.9, 134.0, 136.0, 146.3, 149.8, 169.6; IR (thin film) 1786, 1749, 1726, 1369 cm^{-1}; LRMS 563 (FAB, M + Na); HRMS Calculated for $C_{20}H_{23}F_3O_8S_2Na$ 563.0746 (FAB, M + Na). Found 563.0754.

tert-Butyl 10-(3-Furyl)-1-oxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (159). To a solution of borate **158** (53 mg, 0.47 mmol), Na_2CO_3 (47 mg, 0.43 mmol), water (0.22 mL), LiCl (40 mg, 0.94 mmol) and triflate **153** (170 mg, 0.31 mmol) in DME (4 mL) was added Pd(0)$(PPh_3)_4$ (18 mg, 15.6 μmol) at rt. After stirring for 3 h at 90 °C, the reaction mixture was diluted with EtOAc and the mixture was washed with water. Combined organic layers were washed with water and brine, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 23% EtOAc in *n*-hexane) to afford **159** as slight yellow syrup (116 mg, 80%): R_f = 0.35 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 2.08-2.20 (m, 1H), 2.36-2.45 (m, 1H), 2.70 (dd, J = 11.46, 1.50 Hz, 1H), 3.24 (dd, J = 16.27, 2.11 Hz, 1H), 3.71-3.82 (m, 3H), 4.13 (dd, J = 16.27, 4.98 Hz, 1H), 5.91 (dd, J = 4.98, 2.11 Hz, 1H), 6.34 (dd, J = 1.75, 0.81 Hz, 1H), 7.28 (s, 1H), 7.31 (dd, J = 1.75, 1.58 Hz, 1H), 7.51-7.64 (m, 3H), 7.76 (dd, J = 8.47, 1.52 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 28.4, 43.8, 45.7, 49.9, 52.6, 84.0, 110.2, 123.1, 123.4, 128.0, 129.7, 130.5, 133.6, 135.9, 139.7, 143.5, 150.2, 174.2; IR (thin film) 1778, 1741, 1720, 1367 cm^{-1}; UV (MeOH) ε 201, 265, 271 nm: LRMS 481 (FAB, M + Na); HRMS Calculated for $C_{23}H_{26}N_2O_6SNa$ 481.1409 (FAB, M + Na). Found 481.1445 (FAB, M + Na).

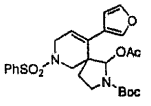


tert-Butyl (3*R**,5*R**,10*S**)-1-Hydroxy-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (161) and *tert*-Butyl (3*R**,5*R**,10*S**)-1-(Acetyloxy)-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (162). A 1.5 M solution of DIBAL-H in toluene (0.5 mL, 0.75 mmol) was added dropwise to a solution of carbamate **159** (98 mg, 0.21 mmol) in toluene (1 mL) and CH_2Cl_2 (1 mL) at −78 °C. The mixture was warmed to 0 °C over 1 h and stirring was continued for at rt. After the solution was cooled to −78 °C, 0.7 M Rochelle's salt (3 mL) was added dropwise and then the mixture was warmed to 0 °C over 10 min and stirred for 1 h at rt. After EtOAc and 0.7 M Rochelle's salt were added, separated organic layer

was washed with 0.7 M Rochelle's salt and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 23% EtOAc in *n*-hexane) to afford aminal **161** (75 mg, 76%). Aminal **161** (75 mg) was dissolved in pyridine (0.2 mL) and acetic anhydride (0.2 mL), and the mixture was stirred for 4 h at rt. Products were partitioned between EtOAc and 1 *N* HCl. Separated organic layer was washed with aq. sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo affording acetate **162** as a colorless syrup (80 mg, 98%). ***tert*-Butyl (3*R**,5*R**,10*S**)-1-Hydroxy-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (161)**: R_f = 0.31 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.38 (m, 1H), 1.49 (s, 18/5H), 1.53 (s, 27/5H), 2.22 (d, J = 12.46 Hz, 3/5H), 2.36-2.51 (m, 7/5H), 3.06 (brs, 3/5H), 3.23-3.67 (m, 20/5H), 3.90 (brs, 2/5H), 4.17 (dd, J = 15.63, 2.79 Hz, 2/5H), 4.22 (dd, J = 16.84, 2.70 Hz, 3/5H), 5.48 (brs, 2/5H), 5.54 (brs, 3/5H), 5.84 (s, 1H), 6.47 (s, 1H), 7.30 (s, 1H), 7.42 (s, 1H), 7.52-7.63 (m, 3H), 7.73-7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 29.6, 30.7, 43.8, 44.2, 45.5, 45.8, 50,1, 50.8, 51.0, 80.9, 81.4, 86.9, 112.4, 124.2, 125.1, 127.9, 128.0, 129.6, 131.9, 133.4, 136.5, 136.4, 141.3, 142.5, 154.5, 155.3; IR (thin film) 3420, 1678, 1394 cm^{-1}.

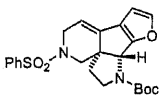


***tert*-Butyl (3*R**,5*R**,10*S**)-1-(Acetyloxy)-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (162)**: R_f = 0.21 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39-1.57 (m, 1H), 1.45 (s, 9H), 1.86 (brs, 3H), 2.41 (d, J = 16.44 Hz, 1H), 2.49-2.60 (m, 1H), 3.40 (dd, J = 17.42, 3.37 Hz, 1H), 3.46-3.62 (m, 2H), 3.66 (d, J = 11.44 Hz, 1H), 4.12 (dd, J = 17.42, 3.37 Hz, 1H), 5.82 (t, J = 3.37 Hz, 1H), 6.36 (t, J = 0.74 Hz, 1H), 6.73 (brs, 1H), 7.31 (s, 1H), 7.32 (d, J = 2.55 Hz, 1H), 7.50-7.62 (m, 3H), 7.75-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 28.7, 29.1, 44.1, 45.5, 50.1, 50.9, 81.4, 86.4, 111.6, 124.9, 125.8, 128.1, 129.6, 129.8, 133.4, 136.9, 140.3, 142.9, 154.1, 169.0; IR (thin film) 1824, 1747, 1704, 1367 cm^{-1}.

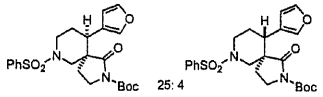


***tert*-Butyl (3a*R**,10b*R**)-5-(Phenylsulfonyl)-2,3,4,5,6,10b-hexahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (163)**. To a solution of acetate **162** (15 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was added *p*-TsOH monohydrate (6 mg, 3.15 μmol) at rt. After stirring for 2 h at rt, the reaction was quenched by addition of sat. $NaHCO_3$ aqueous solution and extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 45% EtOAc in *n*-hexane) to afford **163** (10 mg, 76%) as a colorless syrup: R_f = 0.28 (silica gel,

EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.85-2.15 (m, 1H), 2.25-2.55 (m, 1H), 2.67 (d, J = 10.83 Hz, 1H), 3.34 (brd, J = 16.76 Hz, 0.5H X 2), 3.58 (brt, J = 10.81 Hz, 2H), 3.98 (d, J = 10.8 Hz, 1H), 4.25 (dd, J = 16.76, 3.11 Hz, 1H), 4.69 (brs, 0.5H), 4.83 (brs, 0.5H), 5.43 (t, J = 3.11Hz, 1H), 6.30 (brs, 1H), 7.38 (brs, 1H), 7.52-7.62 (m, 3H), 7.82 (d, J = 6.99 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 34.0, 34.8, 44.9, 45.9, 46.5, 48.9, 59.1, 60.3, 61.7, 80.6, 105.3, 109.7, 126.4, 127.8, 129.6, 133.3, 135.1, 136.9, 148.7, 149.0, 154.6, 155.3, 162.5; IR (thin film) 1697, 1394, 1360, 1167, 1146, 1101 cm^{-1}; LRMS 442 (EI, M^+); HRMS Calcd for $C_{23}H_{26}N_2O_5S$ 442.1562 (EI, M^+). Found 442.1559; LRMS 465 (FAB, M + Na), 481 (FAB, M + K), 575 (FAB, M + Cs); UV (MeOH) 201.5, 227, 265, 271 nm.

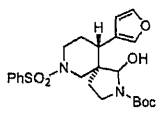


***tert*-Butyl (5*R**,10*S**)-10-(3-Furyl)-1-oxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (167).** To a degassed solution of **159** (185 mg, 0.40 mmol) in EtOH (5 mL) was added Pd on charcoal (205 mg, 10% Pd) at rt. The resulting slurry was hydrogenated over 1 h and filtered. The charcoal was washed with EtOAc (130 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, 9% to 29% EtOAc in *n*-hexane) to afford alcohol **167** as a colorless slid (127 mg, 68%): R_f = 0.28 (silica gel, EtOAc/*n*-hexane, 1:2); mp 167.0-169.0 °C dec. (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 1.57-1.71 (m, 2H), 1.92-2.03 (m, 1H), 2.45 (dd, J = 12.13, 3.89 Hz, 1H), 2.51 (d, J = 12.35 Hz, 1H), 2.55-2.64 (m, 1H), 2.70-2.85 (m, 1H), 3.17-3.25 (m, 1H), 3.41-3.67 (m, 1H), 3.74 (d, J = 11.60, 1.50 Hz, 1H), 3.96 (dd, J = 12.35, 1.50 Hz, 1H), 6.31 (d , J = 1.92 Hz, 1H), 7.28 (brd, J = 1.43 Hz, 1H), 7.32 (brd, J = 1.57 Hz, 1H), 7.54-7.61 (m, 3H), 7.88 (dd, J = 8.00, 1.69 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 28.5, 28.9, 40.5, 42.8, 46.3, 47.9, 52.1, 83.2, 110.9, 124.2, 128.4, 129.4, 133.2, 137.2, 140.7, 143.5, 150.4, 173.1; IR (KBr) 1754, 1712, 1323, 1155 cm^{-1}; Anal. Calcd for $C_{23}H_{28}N_2OS$ C: 59.98, H: 6.13, N: 6.08, O: 20.84, S: 6.96. Found C: 59.79, H: 5.99, N: 5.82 ; LRMS 483 (FAB, M + Na); HRMS Calcd for $C_{23}H_{28}N_2OSNa$ 483.1566 (FAB, M + Na). Found 483.1596; UV (MeOH) 204, 265, 271.5 nm.

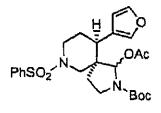


***tert*-Butyl (5*R**,10*S**)-10-(3-Furyl)-1-hydroxy-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (170), *tert*-Butyl (5*R**,10*S**)-1-(Acetyloxy)-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (171) and *tert*-Butyl**

(3a*R,7a*R**,10b*R**)-5-(Phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (169).** A 1.5 M solution of DIBAL-H in toluene (0.5 mL, 0.75 mmol) was added dropwise to a solution of carbamate **167** (100 mg, 0.22 mmol) in toluene (1 mL) and CH_2Cl_2 (1 mL) at –78 °C. The mixture was warmed to 0 °C over 1 h and stirring was continued for 0.5 h at rt. After the solution was cooled to –78 °C, 0.7 M Rochelle's salt (3 mL) was added dropwise and then the mixture was warmed to 0 °C over 10 min and stirred for 1 h at rt. After EtOAc and 0.7 M Rochelle's salt were added, separated organic layer was washed with 0.7 M Rochelle's salt and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 33% EtOAc in *n*-hexane) to afford aminal **170** (54 mg, 54%). Aminal **170** (40 mg) was dissolved in pyridine (0.3 mL) and acetic anhydride (0.3 mL), and the mixture was stirred for 12 h at rt. Products were partitioned between EtOAc and 1 *N*HCl. Separated organic layer was washed with aq. sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo affording acetate **171** as a colorless syrup (57 mg). To a solution of acetate **171** (50 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added *p*-TsOH monohydrate (21 mg, 0.11 mmol) at rt. After stirring for 0.5 h, the reaction was quenched by addition of sat. $NaHCO_3$ aqueous solution and extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 45% EtOAc in *n*-hexane) to afford **169** [18 mg, 53% (2 steps)] as a colorless syrup. ***tert*-Butyl (5*R**,10*S**)-10-(3-Furyl)-1-hydroxy-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (170):** R_f = 0.25 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.65-1.8 (brd, 7/7H), 1.8-2.3 (m, 21/7H), 2.4-2.7 (m, 14/7H), 2.7-3.15 (m, 16/7H), 3.25 (d, J = 11.92 Hz, 5/7H), 3.27-3.51 (m, 14/7H), 3.54-3.66 (brd, 7/7H), 4.48 (d, J = 2.79 Hz, 1H), 6.15 (brs, 5/7H), 6.24 (brs, 2/7H), 7.02 (brs, 5/7H), 7.12 (brs, 2/7H), 7.23 (brs, 5/7H), 7.30 (brs, 2/7H), 7.54-7.75 (m, 3H), 7.77-7.78 (m, 2H); IR (KBr) 1681, 1394 cm^{-1}; LRMS 485 (FAB, M + Na); HRMS Calculated for $C_{23}H_{30}N_2O_6SNa$ 485.1722 (FAB, M + Na). Found 485.1751.

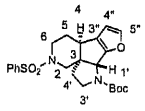


***tert*-Butyl (5*R**,10*S**)-1-(Acetyloxy)-10-(3-furyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (171):** R_f = 0.17 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 & 1.42 (s, 9H), 1.5-3.9 (m, 11H), 1.80 (s, 3/2H), 2.22 (s, 3/2H), 6.00 (brs, 1H), 6.13 (brs, 1H), 6.97 (brs, 1H), 7.24 (brs, 1H), 7.52-7.67 (m, 5H), 7.78-7.88 (m, 2H); IR (KBr) 1731, 1702, 1403 cm^{-1}; LRMS 527 (FAB, M + Na); HRMS Calculated for $C_{25}H_{32}N_2O_7SNa$ 527.1828 (FAB, M + Na). Found 527.1877.

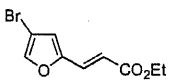


***tert*-Butyl**

(3a*R,7a*R**,10b*R**)-5-(Phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (169)**: R_f = 0.22 (silica gel, EtOAc/*n*-hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.57-1.64 (m, 1H), 1.87-1.92 (m, 2H), 2.01-2.08 (m, 1H), 2.76 (brt, J = 6.33 Hz, 1H), 3.06-3.25 (brm, 2H), 3.08 (d, J = 12.39 Hz, 1H), 3.26-3.75 (m, 2H), 3.34 (d, J = 12.39 Hz, 1H), 4.65 (s, 1H), 6.14 (d, J = 1.80 Hz, 1H), 7.33 (brs, 1H), 7.50-7.63 (m, 3H), 7.77 (dd, J = 8.37, 1.53 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 28.8, 36.3, 39.1, 42.8, 45.3, 50.0, 61.2, 62.5, 80.5, 107.3, 127.7, 128.9, 129.6, 133.1, 137.8, 147.7, 154.8, 157.3; IR (thin film) 1693, 1394 cm^{-1}; LRMS 445 (FAB, M + H); HRMS Calculated for $C_{23}H_{28}N_2O_5SNa$ 467.1617 (FAB, M + H). Found 467.1629; UV (MeOH) 201.8, 222.8, 264.4, 271.5 nm.

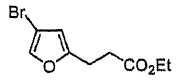


Ethyl (2*E*)-3-(4-Bromo-2-furyl)-2-propenoate (186). To a solution of triethyl phosphonoacetate (7.05 g, 31.45 mmol) in THF (30 mL) was added sodium *t*-butoxide (3.16 g, 32.86 mmol) at 0 °C. After stirring for 30 min at the same temperature, the reaction mixture was stirred for an additional 1 h at rt. The mixture was cooled to 4 °C, a solution of aldehyde **185** (5.0 g, mmol) was added, and stirred for 30 min at the same temperature, and stirred for an additional 1 h at rt. The reaction was quenched by addition of sat. NH_4Cl (20 mL) aqueous solution in an ice-bath and concentrated in vacuo. The residue was dissolved in EtOAc (150 mL), and the solution was washed with water (70 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 0% to 26% EtOAc in *n*-hexane) to afford **186** as a colorless solid (6.74 g, 96%): R_f = 0.48 (silica gel, EtOAc/*n*-hexane, 1:6); mp 46-47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.32 (t, J = 7.14 Hz, 3H), 4.24 (q, J = 7.14 Hz, 2H), 6.33 (d, J = 15.82 Hz, 1H), 6.62 (s, 1H), 7.35 (d, J = 15.82 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 60.6, 101.8, 116.6, 117.8, 129.9, 142.6, 151.5, 166.5; IR (thin film) 3128, 2985, 1707, 1647, 1568, 1495, 1475, 1308, 1282, 1261, 1184, 1140, 1115, 1093, 974, 931, 860, 825, 787, 733, 588, 523 cm^{-1}; LRMS (EI, M$^+$): 244; HRMS Calculated for $C_9H_9O_3Br$ (FAB, M + H): 243.9735. Found 243.9717; Anal. calculated for $C_9H_9O_3Br$ C: 44.11, H: 3.70, O: 19.59, Br: 32.60. Found C: 44.13, H: 3.62.

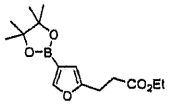


Ethyl 3-(4-Bromo-2-furyl)propanoate (187). To a solution of enone **186** (3.10 g, 12.65 mmol) and $NiCl_2$ (164 mg, 1.27 mmol) in EtOH (40 mL) was added $NaBH_4$ (957 mg, 25.30 mmol) at 0 °C. After stirring for 1 h at the same temperature, insoluble black material was filtered off at 0 °C and the reaction was quenched by addition of water (5 mL) to the filtrate and the mixture was concentrated in vacuo. The residue was

dissolved in EtOAc and the solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0% to 26% EtOAc in *n*-hexane) to afford **187** as a sweet odor oil (3.04 g, 92%): R_f= 0.54 (silica gel, EtOAc/*n*-hexane, 1:6); ^{1}H NMR (300 MHz, $CDCl_3$) 1.25 (t, J = 7.15 Hz, 3H), 2.62 (t, J = 7.72 Hz, 2H), 2.94 (t, J = 7.72 Hz, 2H), 4.15 (q, J = 7.15 Hz, 2H), 6.09 (d, J = 0.80 Hz, 1H), 7.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 23.5, 32.3, 60.7, 99.9, 109.1, 139.5, 155.3, 172.1; IR (thin film): 1736 cm^{-1}; LRMS (EI, M$^+$) 246; HRMS Calculated for $C_9H_{11}O_3Br$ (EI, M$^+$): 245.9892. Found 245.9856.

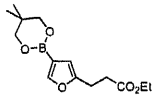


Ethyl 3-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furyl]propanoate (193). To a solution of bromide **187** (1.10 g, 4.45 mmol), bis(pinacolato)diboron (1.24 g, 4.88 mmol) and potassium acetate (1.31 g, 13.35 mmol) in DMSO (8 mL) was added $PdCl_2$(dppf) (98 mg, 0.134 mmol) at rt. After stirring for 5 h at 82 °C, the reaction mixture was diluted with EtOAc and the solution was washed with water and brine. Combined organic layers were concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0% to 9% EtOAc in *n*-hexane) to afford **193** as a yellow solid (1.06 g, 80%): R_f= 0.22 (silica gel, EtOAc/*n*-hexane, 1:6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.11 Hz, 3H), 1.30 (s, 12H), 2.62 (t, J = 7.11 Hz, 2H), 2.96 (t, J = 7.11 Hz, 2H), 4.13 (q, J = 7.11 Hz, 2H), 6.20 (d, J = 0.72 Hz, 1H), 7.63 (d, J = 0.72 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.2, 24.8, 25.0, 32.7, 60.5, 83.4, 83.5, 108.7, 111.4 (MBC spectra enable us to determine this chemical shifts), 150.0, 154.8, 172.4; IR (thin film) 1738 cm^{-1}; LRMS 294 (FAB, M), 333 (FAB, M + K); HRMS (FAB) Calculated for $C_{15}H_{23}O_5B$ 294.1639 (FAB, M). Found 294.1664.

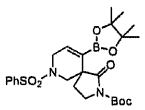


Ethyl 3-[4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-furyl]propanoate (194). To a solution of bromide **187** (13.1 g, 53.01 mmol), bis(neopentyl glycolato)diboron (13.2 g, 58.32 mmol) and potassium acetate (15.61 g, 159.05 mmol) in DMSO (60 mL) was added $PdCl_2$(dppf) (1.16g, 1.59 mmol) at rt. After stirring for 5 h at 82 °C, the reaction mixture was diluted with EtOAc (300 mL) and the mixture was washed with water and brine. Combined organic layers were concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0% to 26% EtOAc in *n*-hexane) to afford **194** as a colorless solid (12.1 g, 82%): R_f= 0.39 (silica gel, EtOAc/*n*-hexane, 1:6); mp 32.5-33.5 °C (non); ^{1}H NMR (300 MHz, $CDCl_3$) 1.00(s, 6H), 1.25 (t, J = 7.14 Hz, 3H), 2.63 (t, J = 7.17 Hz, 2H), 2.96 (t, J = 7.17 Hz 2H), 3.69 (s, 4H), 4.14 (q, J = 7.14 Hz, 2H), 6.16 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 21.9, 23.3, 31.9, 32.7, 60.5, 108.4, 115.5 (HMBC

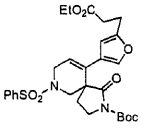
spectra enable us to determine this chemical shifts), 149.0, 154.5, 172.5; IR (thin film): 1736 cm^{-1}; LRMS (EI, M^+) 280; HRMS Calculated for $C_{14}H_{21}O_5B$ (EI, M^+): 280.1482 (279.1519). Found 279.1495; Anal. Calculated for $C_{14}H_{21}O_5B$ C: 60.03, H: 7.56, O: 28.56, B: 3.86. Found C: 60.05, H: 7.76.



***tert*-Butyl 1-Oxo-7-(phenylsulfonyl)-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (198).** To a solution of triflate **153** (740 mg, 1.369 mmol), bis(pinacolato)diboron (386 g, 1.52 mmol) and potassium acetate (403 mg, 4.11 mmol) in dioxoane (9 mL) were added $PdCl_2$(dppf) (30 mg, 41.1 μmol) and DPPF (23 mg) at rt. After stirring for 5 h at 80 °C, the reaction mixture was diluted with EtOAc and the mixture was washed with water and brine. Combined organic layers were concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 34% EtOAc in *n*-hexane) to afford **198** as a yellow solid (303 mg, 43%): R_f = 0.38 (silica gel, EtOAc/*n*-hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.16 (s, 3H), 1.24 (s, 9H), 1.54 (s, 6H), 2.00-2.15 (m, 1H), 2.20-2.30 (m, 1H), 2.50 (dd, J = 11.32, 1.21 Hz, 1H), 3.70 (d, J = 11.32 Hz, 1H), 3.68-3.95 (m, 2H), 3.16 (dd, J = 17.64, 2.06 Hz, 1H), 4.08 (dd, J = 17.64, 4.20 Hz, 1H), 6.53 (dd, J = 4.20, 2.06 Hz, 1H), 7.50-7.60 (m, 3H), 7.72-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 24.75, 24.83, 28.0, 28.8, 43.5, 45.6, 49.0, 50.2, 75.0, 82.7, 84.0, 127.5, 129.2, 130.80 (brs, C-4 elucidated by using HMBC), 133.1, 135.5, 137.9, 150.2, 175.1; LRMS 541 (FAB, M + Na); HRMS Calculated for $C_{25}H_{35}BN_2O_7SNa$ 541.2160 (FAB, M + Na). Found 541.2169.

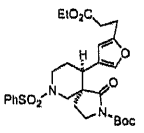


***tert*-Butyl 10-[5-(3-Ethoxy-3-oxopropyl)-3-furyl]-1-oxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]dec-9-ene-2-carboxylate (200).** To a solution of borate **194** (607 mg, 2.17 mmol), Na_2CO_3 (242 mg, 2.28 mmol), water (0.7 mL), LiCl (207 mg, 4.88 mmol) and triflate **153** (881 mg, 1.63 mmol) in DME (8 mL) was added Pd(0)$(PPh_3)_4$ (18 mg, 15.6 μmol) at rt. After stirring for 7 h at 80 °C, the reaction mixture was diluted with EtOAc. Combined organic layers were washed with water and brine, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 0% to 30% EtOAc in *n*-hexane) to afford **200** as slight yellow foam [615 mg, 68% (2 steps)]: R_f = 0.24 (silica gel, EtOAc/*n*-hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.12 Hz, 3H), 1.55 (s, 9H), 2.02-2.18 (m, 1H), 2.32-2.45 (m, 1H), 2.59 (t, J = 7.23 Hz, 2H), 2.69 (dd, J = 11.53, 1.34 Hz, 1H), 2.89 (dt, J = 7.23, 0.77 Hz, 2H), 3.25 (dd, J = 16.79, 2.04 Hz, 1H), 3.75-3.81 (m, 3H), 4.13 (q, J = 7.12 Hz, 2H), 4.10-4.16 (m, 1H), 5.89 (dd, J = 4.95, 2.04



Hz, 1H), 6.00 (d, J = 0.77 Hz, 1H), 7.14 (s, 1H), 7.52-7.63 (m, 3H), 7.75-7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.3, 27.4, 28.0, 32.5, 43.3, 45.3, 49.5, 52.1, 60.6, 83.6, 105.5, 122.2, 123.5, 127.6, 129.3, 130.2, 133.2, 135.5, 137.8, 149.8, 154.8, 172.3, 173.9; IR (thin film) 1780, 1728 cm^{-1}; LRMS 581 (FAB, M + Na); HRMS Calculated for $C_{20}H_{34}N_2O_8SNa$ 581.1934 (FAB, M + Na). Found 581.1932.

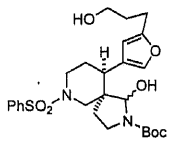
tert-Butyl (5*R**,10*S**)-10-[5-(3-Ethoxy-3-oxopropyl)-3-furyl]-1-oxo-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (202). To a degassed solution of **200** (130 mg, 0.23 mmol) in EtOH (15 mL) was added Pd on charcoal (200 mg, 10% Pd) at rt. The resulting slurry was hydrogenated over 1.5 h and filtered. The charcoal was washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, 9% to 30% EtOAc in *n*-hexane) to afford **202** as a colorless slid (112 mg, 86%): R_f = 0.22 (silica gel, EtOAc/*n*-hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, J = 7.15 Hz, 3H), 1.40-1.52 (m, 1H), 1.44 (s, 9H), 1.54-1.57 (m, 1H), 1.85-1.95 (m, 1H), 2.29 (dd, J = 12.03, 3.76 Hz, 1H), 2.42 (d, J = 12.32 Hz, 1H), 2.45-2.54 (m, 1H), 2.50 (t, J = 7.22 Hz, 2H), 2.59-2.73 (m, 1H), 2.80 (t, J = 7.22 Hz, 2H), 3.12-3.10 (m, 1H), 3.38-3.58 (m, 1H), 3.78-3.82 (brt, 1H), 3.87 (dd, J = 12.32, 1.35 Hz, 1H), 4.06 (q, J = 7.15 Hz, 2H), 5.86 (s, 1H), 7.06 (s, 1H), 7.44-7.53 (m, 3H), 7.78-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.5, 27.8, 28.1, 28.5, 32.6, 40.3, 42.4, 45.9, 47.4, 51.7, 60.5, 82.8, 106.3, 124.4, 127.9, 129.0, 132.8, 136.9, 138.8, 150.0, 154.9, 172.3, 172.7; IR (thin film) 1778, 1735, 1712 cm^{-1}; MS 583 (FAB, M + Na); HRMS Calculated for $C_{28}H_{36}N_2O_8SNa$ 583.2029 (FAB, M + Na). Found 583.2096.

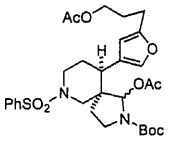


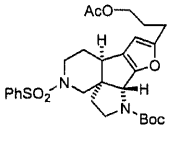
tert-Butyl (5*R**,10*S**)-10-[5-(3-Ethoxy-3-oxopropyl)-3-furyl]-1-hydroxy-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (203), *tert*-Butyl (5*R**,10*S**)-1-(Acetyloxy)-10-[5-(3-ethoxy-3-oxopropyl)-3-furyl]-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (204) and *tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (205). A 1.5 M solution of DIBAL-H in toluene (0.75 mL, 1.13 mmol) was added dropwise to a solution of carbamate **202** (100 mg, 0.19 mmol) in toluene (1 mL) and CH_2Cl_2 (1 mL) at −78 °C. The mixture was warmed to 0 °C over 1 h and stirring was continued for 0.5 h at rt. After the solution was cooled to −78 °C, 0.7 M Rochelle's salt was added dropwise and then the mixture was warmed to 0 °C over 10 min and stirred for 1 h at rt. After EtOAc

and 0.7 M Rochelle's salt were added, separated organic layer was washed with 0.7 M Rochelle's salt and brine, dried over $MgSO_4$ and concentrated in vacuo affording aminal **203** as a colorless syrup (97 mg). Aminal **203** (97 mg) was dissolved in pyridine (1 mL) and acetic anhydride (1 mL), and the mixture was stirred for 12 h at rt. Products were partitioned between EtOAc and 1 *N* HCl were added. Separated organic layer was washed with sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$ and concentrated in vacuo affording acetate **204** as a colorless syrup (94 mg).

To a solution of acetate **204** (94 mg, 0.17 mmol) in CH_2Cl_2 (4 mL) was added *p*-TsOH monohydrate (30 mg, 0.16 mmol) at rt. After stirring for 0.5 h at rt, the reaction was quenched by addition of sat. $NaHCO_3$ aqueous solution and extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 38% EtOAc in *n*-hexane) to afford **205** [47 mg, 49% (3 steps)]: ***tert*-Butyl (5*R**,10*S**)-10-[5-(3-Ethoxy-3-oxopropyl)-3-furyl]-1-hydroxy-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (203)**: R_f = 0.14 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-3.50 (m, 18H), 1.47 (s, 9H), 3.50-3.65 (m, 2H), 4.85 (m, 2/5H), 5.76-6.01 (m, 3/5H), 6.86-7.27 (m, 1H), 7.50-7.65 (m, 3H), 7.74-7.87 (m, 2H); LRMS 520 (FAB, M); HRMS Calculated for $C_{26}H_{36}N_2O_7S$ 520.2243 (FAB, M + Na). Found 520.2294. ***tert*-Butyl (5*R**,10*S**)-1-(Acetyloxy)-10-[5-(3-ethoxy-3-oxopropyl)-3-furyl]-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylate (204)**: R_f = 0.48 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2-3.90 (m, 15H), 1.39-1.47 (m, 9H), 1.81 (s, 3/3H), 2.04 (s, 3H), 2.22 (s, 6/3H), 4.00-4.13 (m, 2H), 4.87-6.16 (m, 2H), 6.80-7.20 (m, 1H), 7.53-7.63 (m, 3H), 7.75-7.87 (m, 2H); LRMS 627 (FAB, M + Na); HRMS Calculated for $C_{30}H_{40}N_2O_9SNa$ 627.2352 (FAB, M + Na). Found 627.2390. ***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (205)**: R_f = 0.46 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.45-1.60 (m, 1H), 1.74-2.04 (m, 5H), 2.04 (s, 3H), 2.66 (t, J = 7.46 Hz, 2H), 2.72 (t, J = 6.12 Hz, 1H), 3.07-3.15 (m, 3H), 3.36-3.46 (m, 2H), 3.52-3.59 (m, 1H), 4.10 (t, J = 6.28 Hz, 2H), 4.62 (brs, 1H), 5.79 (s, 1H), 7.50-7.63 (m, 3H), 7.75-7.79 (m, 2H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 20.9, 25.4, 27.0, 28.4, 35.9, 36.6, 39.1, 42.3, 44.8, 49.5, 60.4, 62.4, 63.5, 79.9, 102.7, 127.2, 128.9, 129.1, 132.7, 137.4, 154.3, 155.1, 160.1, 171.0; IR (thin film) 1737, 1695 cm^{-1}; LRMS 567

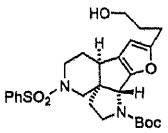






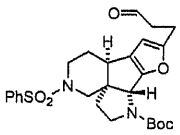
(FAB, M + Na); HRMS Calculated for $C_{28}H_{36}N_2O_7SNa$ 567.2141 (FAB, M + Na). Found 567.2143.

***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Hydroxypropyl)-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (206).** To a solution of ester **205** (40 mg, 73.4 μmol) in MeOH (1 mL) was added 1 *N* NaOH (1 mL, 1.00 mmol) at rt. After stirring for 0.5 h at rt, the reaction mixture was concentrated in vacuo and extracted with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 90% to 100% EtOAc in *n*-hexane) to afford alcohol **206** as a colorless solid (34 mg, 92%): R_f = 0.11 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.74 (m, 1H), 1.53 (s, 9H), 1.87-2.06 (m, 5H), 2.68 (t, J = 7.47 Hz, 2H), 2.72 (brt, J = 6.14 Hz, 1H), 3.07-3.45 (m, 5H), 3.52-3.61 (m, 1H), 3.67 (brq, J = 5.96 Hz, 2H), 4.62 (s, 1H), 5.78 (s, 1H), 7.49-7.62 (m, 3H), 7.75-7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.9, 28.4, 35.9, 39.1, 42.2, 44.8, 49.5, 60.4, 61.9, 62.4, 79.9, 102.4, 127.2, 128.9, 129.2, 132.7, 137.4, 154.3, 155.0, 160.9; IR (thin film) 3400, 1685 cm^{-1}; LRMS 525 (FAB, M + Na); HRMS Calculated for $C_{26}H_{34}N_2O_6SNa$ 525.2035 (FAB, M + Na). Found 525.2069.

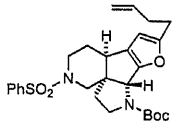


***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Oxopropyl)-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (207) and *tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Butenyl)-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (208).** To a solution of alcohol **206** (160 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (227 mg, 5.35 mmol) at 3 °C. After stirring for 2 h at 3 °C, the reaction was quenched by addition of 1 *N* $Na_2S_2O_3$ (4 mL) and extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 23% to 60% EtOAc in *n*-hexane) to afford aldehyde **207** as a colorless solid (154 mg, 97%). A 0.5 M solution of potassium bis(trimethylsilyl)amide (3 mL, 1.50 mmol) in toluene was added dropwise to a solution of methyltriphenylphosphonium bromide (360 mg, 1.01 mmol) in toluene (1 mL) at 0 °C, and stirred at the same temperature for 0.5 h to give the Wittig solution. To a solution of aldehyde **207** (154 mg, 0.31 mmol) in THF (1 mL) was added dropwise the Wittig

solution (1.5 mL) at 0 °C for 2 h. After stirring for 1 h at rt, the reaction was quenched by addition of sat. NH_4Cl aqueous solution in an ice-bath. The mixture was concentrated in vacuo and dissolved in EtOAc. The mixture was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 9% to 56% EtOAc in *n*-hexane) to afford **208** as a colorless solid [72 mg, 43% (2steps)]: ***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Oxopropyl)-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (207)**: R_f= 0.26 (silica gel, EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.5-1.75 (m, 1H), 1.53 (s, 9H), 1.75-2.04 (m, 3H), 2.69 (t, 1H), 2.72 (t, J = 6.15 Hz, 2H), 2.78 (t, J = 7.18 Hz, 2H), 3.0-3.5 (m, 5H), 3.5-3.7 (m, 1H), 4.63 (s, 1H), 5.80 (s, 1H), 7.50-7.63 (m, 3H), 7.75-7.79 (m, 2H), 9.81 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 27.0, 28.5, 36.0, 39.1, 41.8, 42.3, 44.8, 49.5, 60.4, 62.4, 79.9, 103.1, 127.2, 129.0, 129.1, 132.7, 137.5, 154.3, 155.5, 158.9, 200.6; IR (KBr) 1724, 1693 cm^{-1}; LRMS 494 (FAB, M + Na); HRMS Calculated for $C_{26}H_{33}N_2O_6S$ 501.2059 (FAB, M + Na). Found 501.1983.

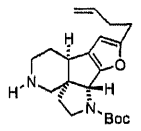


***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Butenyl)-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (208)**: R_f= 0.61 (silica gel, EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.5-1.67 (m, 1H), 1.54 (s, 9H), 1.71-2.06 (m, 3H), 2.37 (q, J = 7.51 Hz, 2H), 2.67 (t, J = 7.88 Hz, 2H), 2.72 (t, J = 5.91 Hz, 1H), 3.08-3.55 (m, 5H), 3.56-3.61 (m, 1H), 4.61 (s, 1H), 4.97-5.08 (m, 2H), 5.76 (s, 1H), 5.78-5.87 (m, 1H), 7.49-7.60 (m, 3H), 7.75-7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.0, 28.5, 32.0, 36.0, 39.2, 42.3, 44.8, 49.6, 60.4, 62.4, 79.9, 102.4, 115.3, 127.3, 128.8, 129.1, 132.7, 137.4, 137.5, 154.4, 155.0, 160.9; IR (KBr) 1691 cm^{-1}; LRMS 521 (FAB, M + Na); HRMS Calculated for $C_{27}H_{34}N_2O_5SNa$ 521.2086 (FAB, M + Na). Found 521.2089.

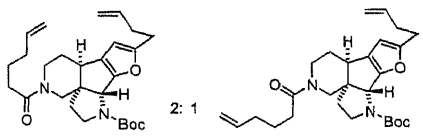


***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Butenyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (209)**. A 0.39 M solution of sodium naphthalenide in DME was prepared by stirring a mixture of sodium metal (409 mg, 17.79 mmol) and naphthalene (2.28 g, 17.79 mmol) in dry DME (40 mL) was stirred for 4 h at rt. The solution maintained a deep blue color. This naphthalenide solution (1.1 mL) was added dropwise to a solution of **208** (70 mg, 0.14 mmol) in DME (8 mL) at –78 °C until a blue color persisted for 30 min. The reaction was quenched by addition of sat. NH_4Cl (5 mL) aqueous solution and concentrated in vacuo. The residue was dissolved in

1 *N*HCl aqueous solution and the solution was washed with EtOAc repeatedly. The aqueous layer was basified to pH 8 with 2 *N*NaOH aqueous solution and extracted with EtOAc. Combined organic layers were washed with 1 *N*NaOH aqueous solution and brine, concentrated in vacuo to give crude amine **209** (31 mg, 62%): R_f= 0.00 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.60 (m, 1H), 1.54 (s, 9H), 1.69-1.78 (m, 1H), 1.96-2.06 (m, 2H), 2.2- 2.4 (brs, 1H), 2.40 (q, J = 7.40 Hz, 2H), 2.52-2.58 (m, 1H), 2.65-2.74 (m, 3H), 2.78 (d, J = 12.97 Hz, 1H), 2.81-2.88 (m, 1H), 3.13 (d, J = 12.97 Hz, 1H), 3.32-3.56 (m, 2H), 4.64 (brs, 1H), 4.97-5.06 (m, 2H), 5.82 (s, 1H), 5.78-5.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 (2C), 30.1, 32.1, 35.9, 38.6, 43.3, 45.3, 52.3, 58.7, 62.0, 79.5, 102.6, 115.1, 130.9, 137.5, 154.7, 155.5, 159.9; IR (thin film) 3400, 2976, 2929, 2873, 2811, 1693, 1398, 1365, 1171, 1122 cm^{-1}; LRMS 359 (FAB, M + H), 397 (FAB, M + K); HRMS Calculated for $C_{21}H_{31}N_2O_3$ 359.2335 (FAB, M + H). Found 359.2381.

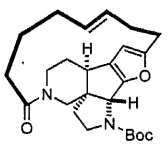


***tert*-Butyl (3a*R**,7a*R**,10b*R**)-9-(3-Butenyl)-5-(5-hexenoyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (211).** To a solution of 5-hexenoic acid (15 mg, 0.129 mmol), HOBt (16 mg, 0.117 mmol) and amine **209** (42 mg, 0.12 mmol) in DMF (1 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC・HCl) (27 mg, 0.14 mmol) at 3 °C for 0.5 h. After stirring for 2 h at rt, the reaction was quenched by addition of water (3 mL) and extracted with EtOAc. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 28% to 45% EtOAc in *n*-hexane) to afford amide **211** as a colorless oil (37 mg, 70%). According to ^{1}H NMR, this compound was observed as a 2:1 mixture of amide rotamer: R_f= 0.41 (silica gel, EtOAc/*n*-hexane, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.42 (m, 6/3H), 1.52 (brs, 27/3H), 1.77-1.95 (m, 12/3H), 2.02-2.07 (m, 6/3H), 2.22 (t, J = 7.46Hz, 4/3H), 2.32 (t, J = 7.46 Hz, 2/3H), 2.38 (brdd, J = 14.45, 6.86 Hz, 6/3H), 2.69 (t, J = 7.77 Hz, 6/3H), 2.76-2.85 (m, 3/3H), 3.20-3.63 (m, 16/3H), 3.96 (brd, J = 13.59 Hz, 2/3H), 4.54 (brs, 2/3H), 4.67 (brs, 1/3H), 4.93-5.08 (m, 12/3H), 5.68-5.91 (m, 6/3H), 5.81 (s, 3/3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 24.2, 28.4, 28.5, 29.7, 31.9, 32.0, 32.4, 32.7, 33.15, 33.20, 36.30, 36.6, 39.8, 40.3, 41.2, 44.3, 44.5, 48.5, 60.9, 62.5, 62.7, 79.8, 80.1, 102.3, 102.4, 115.1, 115.3, 115.3, 128.4, 129.0, 137.3, 137.9, 138.0, 154.1, 154.3, 154.4, 155.0, 161.2, 161.4, 172.6, 173.4; IR (thin film) 2976, 2927, 2871, 1695, 1641, 1394, 1365, 1279, 1257, 1240, 1167, 1109, 912 cm^{-1}; LRMS (FAB, M + Na): 477;

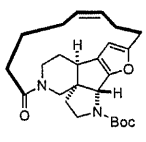


HRMS Calculated for $C_{27}H_{38}N_2O_4$ (FAB, M + Na): 477.2729. Found 477.2781.

***tert*-Butyl (3a*R**,7a*R**,10b*R**,13*E*)-18-Oxo-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-[3]octenofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate [(24*E*)-212] and *tert*-Butyl (3a*R**,7a*R**,10b*R**,13*Z*)-18-Oxo-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-[3]octenofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate [(24*Z*)-212].** A solution of diene **211** (18.0 mg, 39.6 μmol) in degassed (three freeze-thaw cycles) CH_2Cl_2 (80 mL) containing catalyst **214** (4.9 mg, 5.94 μmol) was heated under reflux for 24 h. The reaction mixture was passed through a short pad of silica gel and the filtrate was evaporated to give crude products which was purified by flash column chromatography (silica gel, 9% to 75% EtOAc in *n*-hexane) to afford (24*E*)-**212** 8.4 mg (50%) and (24*Z*)-**212** 6.2 mg (37%) as a colorless oil. ***tert*-Butyl (3a*R**,7a*R**,10b*R**,13*E*)-18-Oxo-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-[3]octenofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate [(24*E*)-212] [Major (Less Polar)]:** R_f = 0.30 (silica gel, EtOAc/*n*-hexane, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (brs, 10H), 1.64-1.78 (m, 4H), 1.84-1.95 (m, 3H), 1.99-2.09 (m, 1H), 2.10-2.18 (m, 1H), 2.23-2.28 (m, 1H), 2.48-2.57 (m, 1H), 2.59-2.69 (m, 1H), 2.74-2.82 (m, 1H), 2.91 (d, J = 12.17 Hz, 1H), 3.02 (brm, 1H), 3.20-3.30 (m, 1H), 3.24-3.38 (m, 2H), 3.45-3.57 (m, 1H), 4.60 (d, J = 12.17 Hz, 1H), 4.67 (s, 1H), 5.06-5.16 (m, 1H), 5.20-5.29 (m, 1H), 5.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.8, 28.3, 28.4, 29.4, 29.7, 31.0, 31.6, 33.3, 39.5, 40.6, 44.3, 45.0, 63.1, 63.3, 79.4, 102.9, 128.5, 130.1, 131.6, 154.0, 156.5, 160.2, 172.7; IR (thin film) 2964, 2927, 2873, 1693, 1645, 1427, 1402, 1365, 1350, 1261, 1169, 1126, 1078, 1022, 800, 740 cm^{-1}; LRMS (FAB, M + Na): 449; HRMS Calculated for $C_{25}H_{34}N_2O_4$ (FAB, M + Na): 449.2416. Found 449.2483.

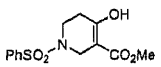


***tert*-Butyl (3a*R**,7a*R**,10b*R**,13*Z*)-18-Oxo-2,3,6,7,7a,10b-hexahydro-1*H*-9,5-[3]octenofuro[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate [(24*Z*)-212] (Minor):** R_f = 0.19 (silica gel, EtOAc/*n*-hexane, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.60 (m, 2H), 1.68-1.78 (m, 4H), 1.88-1.95 (m, 2H), 2.05-2.18 (m, 2H), 2.22-2.37 (m, 1H), 2.47-2.66 (m, 2H), 2.72-2.77 (brd, J = 11.93 Hz, 1H), 2.93 (d, J = 13.64 Hz, 1H), 3.03 (s, 1H), 3.17-3.64 (m, 3H), 3.71-3.78 (m, 1H), 4.62 (d, J = 13.64 Hz, 1H), 4.64 (s, 1H), 5.27 (m, 2H), 5.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 24.0, 25.5, 27.6, 28.3, 29.7, 30.1, 34.1, 39.6, 41.1, 44.2, 44.7, 62.3, 63.5, 79.6, 103.4 (2C), 128.9, 131.8, 154.1, 156.1, 160.4, 173.3; IR (thin film) 2962, 2925, 2870, 1695, 1637, 1402, 1365, 1259, 1167, 1126, 951, 731 cm^{-1}; LRMS (FAB, M + Na): 449; HRMS Calculated for

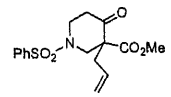


$C_{25}H_{34}N_2O_4Na$ (FAB, M + Na): 449.2416. Found 449.2456.

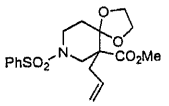
Methyl 4-Hydroxy-1-(phenylsulfonyl)-1,2,5,6-tetrahydro-3-piridinecarboxylate (130). To a stirred solution of $NaHCO_3$ (190.90 g, 2.37 mol) and methyl 4-oxo-3-piperidinecarboxylate hydrochloride **129** (200 g, 1.03 mol) in water (1.6 L) and EtOAc (3.0 L), was added benzenesulfonyl chloride (191.6 g, 1.09 mol) at rt and the mixture was stirred vigorously for 2 h at rt. The organic layer was separated, washed with water (1.0 L, twice) and concentrated in vacuo. The residue was crystallized from diisopropyl ether (120 mL). The resulting solid was collected by filtration, washed with diisopropyl ether and dried at 50 °C in vacuo to give **130** as a colorless solid (286 g, 98%): R_f = 0.41 (silica gel, EtOAc/*n*-hexane, 1:1); mp 88-90 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (t, J = 5.90 Hz, 2H), 3.27 (t, J = 5.90 Hz, 2H), 3.77 (s, 3H), 3.78 (s, 2H), 7.52-7.62 (m, 3H), 7.80-7.84 (m, 2H), 11.93 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 42.09, 42.14, 51.6, 94.8, 127.4, 129.1, 132.9, 136.3, 169.2, 170.3; IR (KBr) 2858, 2827, 1674, 1446, 1348, 1315, 1299, 1228, 958, 722, 752, 578, 563 cm^{-1}; LRMS (EI, M$^+$) 297; Anal. Calculated for $C_{13}H_{15}NO_5S$ C: 52.51, H: 5.08, N: 4.71, O: 26.91, S: 10.78, Found C: 52.64, H: 5.09, N: 4.68.



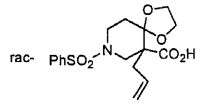
Methyl 3-Allyl-4-oxo-1-(phenylsulfonyl)-3-piperidinecarboxylate (131). To a solution of **130** (100 g, 0.34 mol) in DMF (240 mL) was added a suspension of 60% sodium hydride (16.4 g, 0.41 mol) in oil at 3 °C. After vigorous stirring for 2 h at rt, allyl bromide (30.4 mL, 0.35 mol) was added and the mixture was stirred vigorously for 12 h at rt. The reaction was quenched by addition of water (20 mL) in an ice-bath, extracted with EtOAc (3.4 L). Combined extracts were washed with water (1.0 L, six times) and concentrated in vacuo. The residue was crystallized from diisopropyl ether (400 mL). The resulting solid was collected by filtration, washed with diisopropyl ether (100 mL) and dried at 50 °C in vacuo to give **131** as a colorless solid (193.0 g, 85%): R_f= 0.54 (silica gel, EtOAc/*n*-hexane, 1:1); mp 102.0-103.0 °C dec. (EtOAc/diisopropyl ether): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48-2.61 (m, 3H), 2.82 (d, J = 12.19 Hz, 1H), 2.82-2.91 (m, 1H), 2.90-3.05 (m, 1H), 3.73-3.77 (m, 1H), 3.78 (s, 3H), 4.12 (dd, J = 12.19, 2.31 Hz, 1H), 5.10-5.17 (m, 2H), 5.71-5.77 (m, 1H), 7.55-7.66 (m, 3H), 7.79-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0, 39.2, 46.3, 52.4, 52.6, 60.6, 119.5, 127.4, 129.2, 131.7, 133.1, 136.1, 169.8, 202.4; IR (KBr) 3082, 2982, 1747, 1720, 1448, 1432, 1340, 1250, 1234, 1167, 590 cm^{-1}; Anal. Calculated for $C_{16}H_{19}NO_5S$ C: 56.96, H: 5.68, N: 4.15, O: 23.71, S: 9.50, Found C: 56.96, H: 5.73, N: 3.97; LRMS (EI, M$^+$) 337.



Methyl 6-Allyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (132). A mixture of **131** (200 g, 0.59 mol), ethylene glycol (160 mL), and *p*-TsOH monohydrate (5.8 g, 30.49 mmol) in dry benzene (2.0 L) was heated under reflux for 48 h using a Dean-Stark apparatus. The mixture was then cooled to rt and concentrated in vacuo. The residue was dissolved in EtOAc (2.5 L), and the solution was washed with water (1.0 L, twice) and concentrated in vacuo. The residue was crystallized from EtOAc (150 mL) to give **132** as a colorless solid (212.9 g, 94%): R_f = 0.38 (silica gel, EtOAc/*n*-hexane, 1:1); mp 164.0-165.5 °C dec. (EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65-1.70 (m, 1H), 2.00-2.05 (m, 1H), 2.50-2.60 (m, 1H), 2.60-2.83 (m, 2H), 2.86 (d, J = 12.35 Hz, 1H), 3.60-3.70 (m, 1H), 3.68 (s, 3H), 3.76 (dd, J = 12.35, 2.23 Hz, 1H), 3.83-3.98 (m, 4H), 5.14-5.28 (m, 2H), 5.69-5.75 (m, 1H), 7.54-7.62 (m, 3H), 7.77-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 34.1, 44.3, 47.9, 51.7, 54.7, 64.8, 65.0, 108.4, 119.9, 127.4, 129.1, 131.8, 132.7, 136.0, 171.4; IR (KBr) 2978, 2951, 2914, 1732, 1469, 1448, 1362, 1302, 1220, 1173, 1122, 1065, 1003, 971, 920, 748 cm^{-1}; Anal. Calculated for $C_{18}H_{23}NO_6S$ C: 56.68, H: 6.08, N: 3.67,O: 25.17, S: 8.41, Found C: 56.68, H: 6.07, N: 3.39; LRMS (EI, M^+) 381.

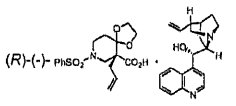


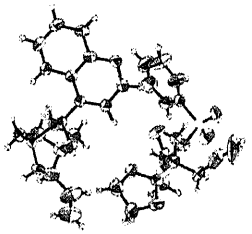
6-Allyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylic Acid (133). To a solution of ester **132** (160.0 g, 0.42 mol) in DMSO (480 mL) was added 8 *N* aqueous solution of NaOH (210 mL) at rt. After stirring mechanically for 2 h at 130 °C, the reaction was quenched by addition of 2 *N* HCl (960 mL) aqueous solution. The resulting solid was collected by filtration, washed with water (400 mL, twice) and EtOAc (400 mL), and dried at 50 °C in vacuo to give racemic acid **133** as a colorless solid (147.0 g, 95%): mp 213.5-214.0 °C dec. (EtOAc/diisopropyl ether); ^{1}H HMR (300 MHz, $CDCl_3$) δ 1.67-1.74 (m, 1H), 1.94-2.04 (m, 1H), 2.50-2.59 (m, 1H), 2.63-2.75 (m, 2H), 2.80 (d, J = 12.41 Hz, 1H), 3.64-3.69 (m, 1H), 3.78 (dd, J = 12.41, 2.00 Hz, 1H), 3.85-4.16 (m, 4H), 5.18-5.32 (m, 2H), 5.70-5.84 (m, 1H), 7.51-7.61 (m, 3H), 7.76-7.79 (m, 2H), 8.5-11.0 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 34.2, 44.2, 47.7, 54.3, 64.8, 64.9, 108.7, 120.7, 127.6, 129.2, 131.0, 132.9, 136.2, 174.1; IR (KBr) 2895, 2858, 1697, 1356, 1342, 1308, 1173, 1142, 1066, 1003, 970, 930, 748, 692, 582 cm^{-1}; Anal. Calculated for $C_{17}H_{21}NO_6S$ C: 55.57, H: 5.76, N: 3.81, O: 26.13, S: 8.73. Found C: 55.46, H: 5.90, N: 3.57; LRMS (FAB) 368 $(M + H)^+$.



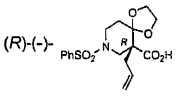
Cinchonium (6*R*)-6-Allyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylate (E-1). A solution of cinchonine (70.9 g, 0.24 mol) and racemic acid **133** (88.5 g, 0.24 mol) in

methanol (1.06 L) was stirred mechanically for 45 min at 70 °C. The mixture was then cooled to rt and stirred for 1 h. The resulting solid was collected by filtration, washed with ethanol (50 mL, twice), and dried at 50 °C in vacuo to give salt **E-1** as a colorless solid (70.0 g, 44% from racemic **133**, 99.7% de): R_f = 0.65 (silica gel, EtOAc); mp 235.0-236.5 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77-0.87 (m, 1H), 1.51-1.72 (m, 1H), 1.82-2.01 (m, 4H), 2.12 (t, J = 8.69 Hz, 1H), 2.47-2.79 (m, 2H), 2.95-3.17 (m, 2H), 3.15 (d, 1H), 3.29-3.54 (m, 4H), 3.79-4.00 (m, 4H), 4.24 (t, J = 11.09 Hz, 1H), 4.99 (d, J = 10.09 Hz, 1H), 5.20-5.27 (m, 3H), 5.90-6.01 (m,2H), 6.33 (brs, 1H), 7.47-7.58 (m, 5H), 7.68-7.78 (m, 4H), 7.97 (d, J = 8.31 Hz, 1H), 8.14 (d, J = 8.41 Hz, 1H), 8.92 (d, J = 4.25 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 23.7, 27.6, 32.0, 34.9, 37.7, 44.7, 48.5, 48.9, 50.1, 55.1, 60.0, 65.0, 65.1, 66.6, 109.6, 117.1, 117.9, 119.2, 122.5, 124.8, 127.0, 127.6, 129.0, 129.1, 130.5, 132.5, 136.61, 136.63, 145.4, 148.1, 150.3, 178.0; IR (KBr) 3400, 3200, 3070, 3004, 2958, 2939, 2858, 1637, 1597, 1510, 1462, 1385, 1335, 1319, 1221, 1171, 1144, 1122, 1090, 1047, 997, 974, 953, 924, 802, 751, 719, 696, 661, 633, 584 cm^{-1}; Anal. Calculated for $C_{36}H_{43}N_3O_7S$ 661.80752 C: 65.33, H: 6.55, N: 6.35, O: 16.92, S: 4.85. Found C: 65.37, H: 6.80, N: 6.26; $[\alpha]_D^{20}$ +63.5° (*c* 0.50, MeOH); Crystal data: $C_{36}H_{43}N_3O_7S$, FW=661.81, orthorhombic system, a = 10.612 (2) Å, b = 15.229 (3) Å, c = 20.949 (4) Å, V = 3385 (1) Å^3, space group $P2_12_12_1$ (#19), Z value = 4, D_{calc} = 1.298 g/cm^3, F_{000} = 1408.00, μ (MoKα) 1.49 cm^{-1}, Lattice constants and intensity data were measured using graphite monochromated MoKα (λ = 0.71069 Å) radiation on graphite monochromated diffractometer. Of the 20390 reflections which were collected, 4480 were unique (R_{int} = 0.065). These were made on a Rigaku/MSC Mercury diffractometer. The structure was solved by direct methods using SIR97 and refined to a final R value of 0.052 and Rw = 0.059.



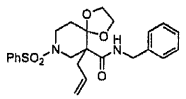


(6*R*)-6-Allyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxylic Acid [(6*R*)-133]. To a suspension of salt **E-1** (68.0 g, 0.10 mol, 99.7% de) in EtOAc (1.4 L) was added 2 *N*HCl (123 mL) aqueous solution at rt. After stirring for 0.5 h, the organic layer was separated and washed with 1 *N* HCl (200 mL, twice) aqueous solution and water (200 mL, twice), dried over $MgSO_4$ and concentrated in vacuo to give chiral acid **(6*R*)-133** (37.7 g, 99.8%, 99.7% ee): $[\alpha]_D^{20}$ –53.3° (*c* 0.43, MeOH). Optical purity of **(6*R*)-133** was confirmed by HPLC analysis using a chiral column. A racemic form of **133** was subjected to HPLC analysis (column: Chiralpak AD column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent



n-hexane/MeOH/TFA, 85:15:1; flow rate, 1.0 mL/min; temperature, 25 °C; detector, 254 nm) and peaks due to cinchonine, (6*R*)-(-)-and (6*S*)-(+)-**133** were detected at t_R 5.2, 11.2 and 13.7 min.

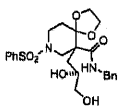
6-Allyl-*N*-benzyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxamide (134). To a solution of **133** (206 g, 0.56 mol), benzylamine (132.2 g, 1.23 mol) and 1-hydroxybenzotriazole (HOBt) (85.9 g, 0.56 mol) in DMF (300 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl) (129.0 g, 675.39 mmol) at 0 °C. After stirring for 2 h at the same temperature, the reaction mixture was heated at 82 °C for 8 h and extracted with EtOAc (1.5 L). Combined organic layers were washed with 2 *N* HCl (500 mL, three times), 2 *N* NaOH (400 mL, twice) and water (500 mL), and concentrated in vacuo. The residue was crystallized from EtOAc (41 mL) and diisopropyl ether (500 mL). The resulting solid was collected by filtration, washed with diisopropyl ether and dried at 50 °C in vacuo to give **134** as a colorless solid (234.0 g, 91%): R_f = 0.45 (silica gel, EtOAc/*n*-hexane, 2:1); mp 161.5-162.0 °C dec. (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (ddd, J = 3.10, 6.74, 13.79 Hz, 1H), 1.90 (ddd, J = 4.88, 11.72, 13.79 Hz, 1H), 2.45 (dd, J = 13.81, 6.93 Hz, 1H), 2.51 (ddd, J = 3.10, 11.72, 14.51 Hz, 1H), 2.77 (dd, J = 13.81, 7.77 Hz, 1H), 2.89 (d, J = 12.50 Hz, 1H), 3.57-3.67 (m, 3H), 3.73-3.88 (m, 3H), 4.19 (dd, J = 4.73, 14.40 Hz, 1H), 4.61 (dd, J = 6.97, 14.40 Hz, 1H), 5.16-5.27 (m, 2H), 5.67-5.27 (m, 1H), 6.75-6.78 (brt, J = 4.73, 6.97 Hz, 1H), 7.23-7.34 (m, 5H), 7.49-7.62 (m, 3H), 7.79 (dd, J = 1.23, 8.42 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.5, 35.8, 43.8, 44.5, 48.5, 53.0, 64.7, 64.8, 109.5, 120.5, 127.9, 128.1, 128.5, 129.1, 130.0, 131.7, 133.1, 136.7, 139.1, 170.8; IR (KBr) 1651 cm^{-1}; Anal. Calculated for $C_{24}H_{28}N_2O_5S$ C: 63.14, H: 6.18, N: 6.14, O: 17.52, S: 7.02. Found C: 63.11, H: 6.20, N: 5.99; LRMS (FAB, M + H): 457.



Optically pure **(6*R*)-134** was prepared as same as racemic **134**. **(6*R*)-6-Allyl-*N*-benzyl-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxamide [(6*R*)-134]**: mp 144.5-146.5 °C dec. (EtOAc/diisopropyl ether); Anal. Calculated for $C_{24}H_{28}N_2O_5S$ C: 63.14, H: 6.18, N: 6.14, O: 17.52, S: 7.02. Found C: 63.15, H: 6.11, N: 6.22; $[\alpha]_D^{20}$ +30.0° (*c* 0.43, $CHCl_3$). Optical purity of **134** was confirmed in by HPLC analysis using a chiral column. A racemic form of **134** was subjected to HPLC analysis (column: Chiralcel OJ column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent EtOH; flow rate, 1.0 mL/min; temperature, 25 °C; detector, 254 nm) and peaks due to (6*S*)-(-)-and (6*R*)-(+)-**134** were detected at t_R 4.8 and 5.7 min.

***N*-Benzyl-6-(2,3-dihydroxypropyl)-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-**

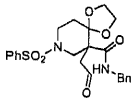
6-carboxamide (215). To a solution of **134** (45 g, 98.56 mmol) and OsO_4 (1.0 g, 3.93 mmol) in THF/water (3:1, 600 mL) was added dropwise 50% aqueous 4-methylmorpholine *N*-oxide (NMO) (45 mL) at 3 °C for 1 h. After stirring for 24 h at rt, the reaction was quenched by addition of 5*N* $Na_2S_2O_4$ (100 mL) aqueous solution and concentrated in vacuo to give solid, which was collected by filtration. The solid was washed with EtOAc (200 mL, three times) and water (200 mL, three times) and dried at rt in vacuo to give **215** as a colorless solid (40 g, 83%). The filtrate was extracted with EtOAc (600 mL), and combined organic layers were washed with brine, and dried over $MgSO_4$. The solvent was concentrated in vacuo to give **215** as a colorless solid (7 g, 14%): R_f= 0.22 (silica gel, EtOAc); mp 204.0-205.0 °C dec. (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 2.28 Hz, 1H), 1.66-1.76 (m, 1H), 1.84-2.09 (m, 3H), 2.68 (brt, J = 8.84 Hz, 1H), 2.80-2.91 (brs, 1H), 3.15 (brd, J = 11.46 Hz, 1H), 3.41-3.53 (m, 3H), 3.61-3.88 (m, 6H), 4.00-4.07 (m, 1H), 4.12 (dd, J = 14.48, 4.57 Hz, 1H), 4.65 (dd, J = 14.48, 4.57 Hz, 1H), 7.02 (brs, 1H), 7.22-7.34 (m, 1H), 7.50-7.63 (m, 3H), 7.77-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 34.3, 43.6, 44.1, 48.8, 51.2, 64.3, 64.6, 67.1, 67.6, 109.2, 127.5, 127.6, 128.0, 128.7, 129.2, 132.9, 136.2, 138.5, 172.1; IR (thin film) 3620, 2875, 2846, 1643, 1533, 1444, 1348, 1232, 1176, 1082, 1063, 1003, 964, 926, 773, 752, 706, 579 cm^{-1}; LRMS (FAB, M + H): 491; HRMS Calculated for $C_{24}H_{31}N_2O_7S$ (FAB, M + H): 491.1852. Found 491.1844; Anal. Calculated for $C_{24}H_{30}N_2O_7S$. 1/2 H_2O C: 57.70, H: 6.25, N: 5.61, O: 24.02, S: 6.42. Found C: 57.80, H: 6.38, N: 5.64.



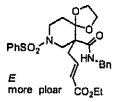
***N*-Benzyl-6-(2-oxoethyl)-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxamide (135), Ethyl (2*E*)-4-[6-[(Benzylamino)carbonyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]dec-6-yl]-2-butenoate [(2*E*)-136], Ethyl (2*Z*)-4-[6-[(Benzylamino)carbonyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]dec-6-yl]-2-butenoate [(2Z)-136], Ethyl [(6*S**,9*R**)-8-Benzyl-7-oxo-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradec-9-yl]acetate (137) and [(6*S**,9*R**)-8-Benzyl-7-oxo-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradec-9-yl]acetic Acid (217).** A solution of $NaIO_4$ (42.3 g, 0.20 mol) in water (500 mL) was added dropwise to a suspension of **215** (65.0 g, 0.13 mol) in CH_2Cl_2 (1 L) at rt and the mixture was stirred for 1 h at rt. The suspension was slowly dissolved with increasing concentration of the product. The reaction was quenched by addition of 5 *N* $Na_2S_2O_4$ (40 mL) aqueous solution. The organic layer was washed with water (500 mL) and brine

(500 mL), dried over $MgSO_4$ and filtered. A small amount of **135** was separated by preparative TLC.

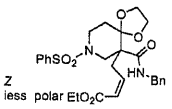
***N*-Benzyl-6-(2-oxoethyl)-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]decane-6-carboxamide (135)**: R_f = 0.23 (silica gel, EtOAc/*n*-hexane, 2:1); mp 174.0-175.5 °C dec. (EtOAc/diisopropyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.85 (m, 2H), 2.78 (dd, J = 16.49, 2.54 Hz, 1H), 2.87 (dd, J = 16.49. 0.00 Hz, 1H), 2.9-3.1 (m, 1H), 3.2-3.35 (m, 1H), 3.35-3.8 (m, 6H), 4.28 (dd, J = 14.56, 5.07 Hz, 6H), 4.55 (dd, J = 14.56, 6.36 Hz, 1H), 6.88 (brs, 1H), 7.15-7.35 (m, 5H), 7.45-7.48 (m, 3H), 7.40-7.79 (m, 2H), 9.68 (brt, J = 2.54 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 43.7, 44.0, 44.5, 49.8, 51.8, 64.4, 64.9, 108.0, 127.6, 127.6, 128.0, 128.7, 129.2, 133.0, 136.4, 138.3, 169.6, 198.7; IR (KBr) 3345, 2929, 2881, 2852, 1720, 1647, 1533, 1446, 1354, 1178, 1157, 1103, 1190, 1066, 1030, 1007, 968, 775, 748, 594, 577 cm^{-1}; LRMS (FAB, M + H): 459; HRMS Calculated for $C_{23}H_{27}N_2O_6S$ (FAB, M + H): 459.1590. Found 459.1570.



(Carbetoxymethylene)triphenylphosphorane (36.0 g, 103.23 mmol) was added to the filtrate and the mixture was concentrated in vacuo to one-third of its volume and then hearted at 50 °C for 1 h. The mixture was washed with brine and concentrated in vacuo to give the residue. A small amount of **136** was separated by preparative TLC. **Ethyl (2*E*)-4-[6-[(Benzylamino)carbonyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]dec-6-yl]-2-butenoate [(2*E*)-136]**: R_f= 0.79 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.13 Hz, 3H), 1.66-1.73 (m, 1H), 1.82-1.93 (m, 1H), 2.54-2.64 (m, 2H), 2.82-2.90 (dd, J = 14.25, 8.16 Hz, 1H), 3.01 (d, J = 12.48 Hz, 1H), 3.57-3.74 (m, 4H), 3.77-3.90 (m, 2H), 4.20 (q, J = 7.13 Hz, 2H), 4.23 (dd, J = 14.40, 4.75 Hz, 1H), 4.59 (dd, J = 14.40, 6.90 Hz, 1H), 5.98 (d, J = 15.53 Hz, 1H), 6.77-6.88 (m, 2H), 7.22-7.34 (m, 5H), 7.49-7.62 (m, 3H), 7.77-7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 30.2, 33.8, 43.5, 44.0, 48.5, 52.5, 60.3, 64.3, 64.5, 108.8, 126.0, 127.5, 127.6, 128.1, 128.7, 129.1, 132.8, 136.2, 138.5, 141.4, 165.9, 169.7; IR (thin film) 3390, 2979, 2937, 2902, 1716, 1662, 1525, 1446, 1356, 1338, 1317, 1286, 1265, 1223, 1171, 1090, 1030, 970, 930, 750, 735, 692, 580 cm^{-1}; LRMS (FAB, M + H): 529; HRMS Calculated for $C_{27}H_{33}N_2O_7S$ (FAB, M + H): 529.2009. Found 529.2069.

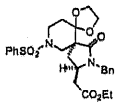


Ethyl (2*Z*)-4-[6-[(Benzylamino)carbonyl]-8-(phenylsulfonyl)-1,4-dioxa-8-azaspiro[4.5]dec-6-yl]-2-butenoate [(2*Z*)-136]: R_f= 0.82 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.14 Hz, 3H), 1.62-1.69 (m, 1H), 1.90-2.00 (m, 1H), 2.53-2.62 (m, 2H), 2.98-3.05 (m, 1H), 3.04 (d, J = 11.99 Hz, 1H), 3.56-3.71 (m, 4H), 3.74-3.88 (m, 3H), 4.02 (m, 3H), 4.51 (dd, J = 14.35, 6.82 Hz, 1H), 5.87 (d, J = 11.55 Hz, 1H), 6.25-6.34 (m, 1H), 7.07 (brt, J = 6.82 Hz, 1H), 7.19-7.31 (m, 5H), 7.49-7.59 (m, 3H), 7.77-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 29.0, 30.5, 43.4, 44.1, 47.9, 52.9,



60.1, 64.6, 64.7, 108.8, 122.4, 127.4, 127.5, 128.1, 128.5, 129.2, 132.8, 136.5, 138.6, 143.2, 166.6, 170.7; IR (thin film) 3394, 2979, 2966, 2929, 2902, 1714, 1662, 1527, 1446, 1356, 1338, 1223, 1186, 1171, 1093, 1028, 968, 924, 804, 750, 735, 692, 579 cm^{-1}; LRMS (FAB, M + H): 529; HRMS Calculated for $C_{27}H_{33}N_2O_7S$ (FAB, M + H): 529.2009. Found 529.2059.

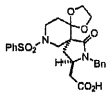
The residue was dissolved in EtOH (450 mL) and DBU (18.0 g, 118.23 mmol), and the solution was refluxed for 1 h. The resulting mixture was concentrated in vacuo and extracted with EtOAc (700 mL). Combined organic layers were washed with 2 *N* HCl (300 mL) and brine (300 mL), and concentrated in vacuo to give the residue. A small amount of **137** was separated by preparative TLC. **Ethyl [(6*S**,9*R**)-8-Benzyl-7-oxo-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradec-9-yl]acetate (137)**: R_f = 0.44 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (q, J = 7.14 Hz, 3H), 1.64-1.71 (m, 1H), 1.90 (dd, J = 13.88, 7.46 Hz, 1H), 1.98-2.09 (m, 1H), 2.36 (dd, J = 15.87, 4.57 Hz, 1H), 2.66 (dd, J = 13.88, 7.58 Hz, 1H), 2.63-2.71 (m, 1H), 2.73 (dd, J = 15.87, 4.57 Hz, 1H), 3.11 (d, J = 11.64 Hz, 1H), 3.51 (dd, J = 11.64, 2.02 Hz, 1H), 3.53-3.66 (m, 1H), 3.71-3.81 (m, 1H), 3.75-4.00 (m, 3H), 3.95-4.03 (m, 1H), 4.04 (d, J = 15.35 Hz, 1H), 4.13 (q, J = 8.15 Hz, 2H), 4.95 (d, J = 15.33 Hz, 1H), 7.18-7.34 (m, 5H), 7.49-7.62 (m, 2H), 7.73-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 32.8, 36.1, 39.5, 44.6, 44.9, 51.5, 51.9, 53.2, 61.3, 65.3, 65.9, 109.9, 127.9, 128.1, 128.2, 129.0, 129.6, 133.3, 136.5, 136.8, 170.7, 172.7; IR (KBr) 2979, 2937, 2900, 2870, 1728, 1678, 1446, 1356, 1167, 1093, 1093, 1030, 970, 744, 692, 594, 576 cm^{-1}; LRMS (FAB, M + H): 529; HRMS Calculated for $C_{27}H_{33}N_2O_7S$ (FAB, M + H): 529.2009. Found 529.2070.



Optically pure **(6*R*,9*S*)-137** was prepared as same as racemic **137**. **Ethyl [(6*R*,9*S*)-8-Benzyl-7-oxo-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradec-9-yl]acetate [(6*R*,9*S*)-137]**: $[\alpha]_D^{20}$ −10.1° (*c* 0.42, $CHCl_3$).

The residue was dissolved in MeOH (450 mL) and 2 *N* NaOH (200 mL) aqueous solution, the mixture was stirred for 1 h at rt and concentrated in vacuo. Resulting residue was dissolved in water (200 mL) and washed with EtOAc (400 mL, twice). Combined organic layers were extracted 1 *N* NaOH (200 mL) aqueous solution. Combined aqueous layers were acidified to pH 2 with 6 *N* HCl, and extracted with EtOAc (350 mL, twice). Combined organic layers were washed with 1 *N* HCl (300 mL, twice) and brine (300 mL, twice), dried over $MgSO_4$, and concentrated in vacuo to give crude acid **217** (50.1 g). A small amount of **217** was separated by preparative TLC. **[(6*S**,9*R**)-8-Benzyl-7-oxo-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradec-9-yl]acetic Acid (217)**: R_f = 0.29 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69

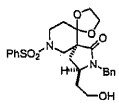
(dm, 1H), 1.92 (dd, J = 13.97, 7.31 Hz, 1H), 1.97-2.07 (m, 1H), 2.39 (dd, J = 16.22, 8.72 Hz, 1H), 2.65 (dd, J = 13.97, 7.75 Hz, 1H), 2.65-2.76 (m, 1H), 2.81 (dd, J = 16.22, 1.17 Hz, 1H), 3.14 (d, J = 11.67 Hz, 1H), 3.51 (dd, J = 11.67, 1.37 Hz, 1H), 3.18-3.90 (m, 5H), 3.91-3.98 (m, 1H), 4.02 (d, J = 15.35 Hz, 1H), 4.98 (d, J = 15.35 Hz, 1H), 7.20-7.31 (m, 5H), 7.51-7.59 (m, 3H), 7.73-7.76 (m, 2H), 8.23 (brs. 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.3, 35.5, 38.5, 44.3, 44.5, 51.2, 51.3, 52.7, 64.8, 65.4, 109.4, 127.5, 127.6, 127.8, 128.6, 129.2, 132.9, 135.7, 136.5, 172.5, 174.8; IR (KBr) 1732, 1685, 1446, 1336, 1169, 1093, 1032, 970, 744, 692, 928, 579 cm^{-1}; LRMS (FAB, M + H): 501; HRMS Calculeted for $C_{25}H_{29}N_2O_7S$ (FAB, M + H): 501.1696. Found 501.1745.



The residue was dissolved in EtOH (450 mL) and acetyl chloride (55.9 g, 0.71 mol) was added dropwise to the solution in an ice-bath. After stirring for 16 h at rt, the reaction mixture was concentrated in vacuo. EtOAc (400 mL) and water (200 mL) were added to the mixture and separated. The organic layer was washed with 1 *N*NaOH and water, dried over $MgSO_4$ and concentrated in vacuo to give crude ester **137**. This crude ester was purified by flash column chromatography (silica gel, 16% to 29% EtOAc in *n*-hexane) to afford ester **137** as a colorless syrup (42.3 g contain H-14 isomer α:β 77:23, 83.8% from amide **134**).

(6*S,9*R**)-8-Benzyl-9-(2-hydroxyethyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one (218).** To a solution of ester **137** (42.3 g, 80.02 mmol, contain H-14 isomer α:β 77:23) in THF (500 mL) was added $LiBH_4$ (3.9 g, 0.18 mol) at 3 °C. After stirring for 1 h at 3 °C, the reaction mixture was stirred for 18 h at rt. The reaction was quenched by addition of 1 *N*HCl (300 mL) aqueous solution, concentrated in vacuo and extracted with EtOAc. Combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc) to afford alcohol **218** as a colorless foam (38.8 g, 99%, contain H-14 isomer α:β 77:23). These diastereomer was separated by flash column chromatography (silica gel, EtOAc) to afford **(6*S**,9*R**)-218** (28.4 g, 73%) and **(6*S**,9*S**)-218** (8.5 g, 22%) as a colorless foam.

(6*S,9*R**)-8-Benzyl-9-(2-hydroxyethyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*S**,9*R**)-218]:** R_f = 0.18 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49-1.57 (m, 1H), 1.61-1.68 (m, 1H), 1.92 (dd, J = 13.74, 7.29 Hz, 1H), 1.97-2.08 (m, 1H), 2.11-2.21 (m, 1H), 2.49 (dd, J = 13.74, 7.61 Hz, 1H), 2.62-2.71 (m, 1H), 3.11 (d, J = 11.65 Hz, 1H), 3.51 (dd, J = 11.65, 2.16 Hz, 1H), 3.59-3.64 (m, 1H), 3.68-3.78 (m, 5H), 3.83-3.88 (m, 2H), 4.02 (1H, d, J = 15.13 Hz, 2H), 4.98 (d, J = 15.13 Hz, 1H), 7.21-7.31 (m, 5H), 7.50-7.60 (m, 3H), 7.72-7.76 (m,



2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.0, 35.7, 36.9, 44.6, 44.8, 51.7, 52.6, 53.4, 59.3, 65.3, 65.9, 109.9, 127.9, 128.3, 128.94, 129.64, 133.3, 136.7, 136.76; 172.7; IR (thin film) 3446, 2937, 2871, 1674, 1446, 1356, 1169, 1093, 1030, 968, 744, 692, 578 cm^{-1}; LRMS (FAB, M + H): 487; HRMS Calculated for $C_{25}H_{31}N_2O_6S$ (FAB, M + H): 487.1903. Found 487.1939; Anal. Calculated for $C_{25}H_{30}N_2O_6S$ 2/3 H_2O, C: 60.87, H: 6.40, N: 5.68, O: 20.54, S: 6.50. Found C: 60.89, H: 6.43, N: 5.62.

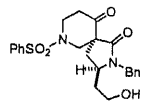
Optically pure (6*R*,9*S*)-218 was prepared as same as racemic (6*S**,9*R**)-218. **(6*R*,9*S*)-8-Benzyl-9-(2-hydroxyethyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*R*,9*S*)-218]**: $[\alpha]_D^{20}$ +9.3° (*c* 0.43, $CHCl_3$). Optical purity of **218** was confirmed by HPLC analysis using a chiral column. A racemic form of **218** was subjected to HPLC analysis (column: Chiralcel OJ column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent EtOH; flow rate, 0.5 mL/min; temperature, 25 °C; detector, 254 nm) and peaks due to (7*S*, 14*S*)-, (7*S*, 14*R*)-, (7*R*, 14*S*)-(+)- and (7*R*, 14*R*)-**218** were detected at t_R 7.9, 8.1, 10.6 and 12.4 min.

(6*S,9*S**)-8-benzyl-9-(2-hydroxyethyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*S**,9*S**)-218]**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.61-1.71 (m, 2H), 1.81-1.93 (m, 2H), 1.97 (dd, J = 13.53, 6.92 Hz, 1H), 1.98-2.09 (m, 1H), 2.32 (dd, J = 13.53, 8.15 Hz, 1H), 2.86-2.94 (m, 1H), 3.16 (d, J = 11.56 Hz, 1H), 3.26 (d, J = 11.56 Hz, 1H), 3.47-3.59 (m, 2H), 3.61-3.72 (m, 2H), 3.85-3.96 (m, 3H), 4.02-4.12 (m, 1H), 4.13 (d, 1H), 4.84 (d, J = 15.01 Hz, 1H), 7.20-7.34 (m, 5H), 7.52-7.60 (m, 3H), 7.72-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 32.5, 35.8, 44.2, 44.7, 50.7, 51.1, 51.4, 58.9, 65.2, 65.6, 108.4, 127.4, 127.6, 127.9, 128.8, 129.2, 132.9, 136.5, 136.6, 172.3; IR (thin film) 3447, 3018, 2891, 1679, 1466, 1357, 1336, 1217, 1167, 1092, 1070, 1031, 1003, 969, 951, 931 cm^{-1}; LRMS (FAB, M + H): 487; HRMS Calculated for $C_{25}H_{31}N_2O_6S$ (FAB, M + H): 487.1903. Found 487.1896.

Optically pure (6*R*,9*R*)-218 was prepared as same as racemic (6*S**,9*S**)-218. **(6*R*,9*R*)-8-Benzyl-9-(2-hydroxyethyl)-12-(phenylsulfonyl)-1,4-dioxa-8,12-diazadispiro[4.0.4.4]tetradecane-7-one [(6*R*,9*R*)-218]**: $[\alpha]_D^{25}$ –100.5° (*c* 1.02, $CHCl_3$).

(3*R,5*S**)-2-Benzyl-3-(2-hydroxyethyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-1,10-dione (219)**. To a solution of ketal **218** (33.8 g, 69.46 mmol, α:β 77:23) in CH_2Cl_2 (746 mL) was added 70% aqueous perchloric acid (70 mL) at rt. After stirring slowly for 2 h, the reaction mixture was carefully pored into aq. sat. $NaHCO_3$ solution. Separated aqueous layers were extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from EtOAc (41 mL) to give **219** as a colorless crystal (21.47 g, 69.8%, corrected yield 91%): R_f = 0.22 (silica

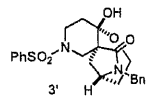
gel, EtOAc/*n*-hexane, 2:1); mp 183.0-186.0 °C dec. (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.55 (m, 1H), 1.62 (brs, 1H), 1.99 (dd, J = 13.81, 8.49 Hz, 1H), 2.04-2.13 (m, 1H), 2.51-2.62 (m, 1H), 2.57 (dd, J = 13.81, 6.92 Hz, 1H), 2.79-2.89 (m, 1H), 2.91-2.97 (m, 1H), 3.39 (d, J = 12.35 Hz, 1H), 3.50-3.60 (m, 1H), 3.61-3.66 (brm, 2H), 3.80 (dd, J = 12.35, 2.59 Hz, 1H), 3.94-4.01 (m, 1H), 4.06 (d, J = 15.34 Hz, 1H), 5.05 (d, J = 15.34 Hz, 1H), 7.26-7.36 (m, 5H), 7.54-7.65 (m, 3H), 7.77-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 37.1, 37.5, 44.7, 45.5, 52.3, 53.6, 58.7, 59.2, 127.5, 127.6, 127.8, 128.7, 129.4, 133.3, 135.4., 136.1, 170.9, 204.1; IR (KBr) 3465, 1716, 1674, 1362 cm^{-1}; HRMS Calculated for $C_{23}H_{27}O_5N_2S$ (FAB, M + H): 443.1641, Found 443.1620; Anal. Calculated for $C_{23}H_{27}O_5N_2S$. 1/2 H_2O, C: 61.18, H: 6.03, N: 6.20, O: 19.49, S: 7.10. Found C: 61.56, H: 5.99, N: 6.28.



Optically pure (3*S*,5*R*)-**219** was prepared as same as racemic **219**. **(3*S*,5*R*)-2-Benzyl-3-(2-hydroxyethyl)-7-(phenylsulfonyl)-2,7-diazaspiro[4.5]decane-1,10-dione** [(3*S*,5*R*)-**219**]: $[\alpha]_D^{20}$ –33.7° (*c* 0.37, $CHCl_3$).

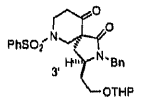
A small amount of **232** was separated by preparative TLC (silica gel, EtOAc) from the filtrate.

(4*S,6a*S**,10a*S**)-5-Benzyl-10a-hydroxy-8-(phenylsulfonyl)octahydro-6*H*,7*H*-4,6a-methanopyrido[4,3-b][1,5]oxazocin-6-one (232), Less Polar (Minor Epimer)**: R_f = 0.55 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73-1.90 (m, 3H), 1.91-2.01 (m, 1H), 2.12 (dd, J = 12.86, 7.11 Hz, 1H), 2.32 (d, J = 12.86 Hz, 1H), 2.46-2.55 (m, 1H), 2.90 (d, J = 12.21 Hz, 1H), 3.45-3.62 (m, 2H), 3.54 (dd, J = 12.21 Hz, 1H), 3.68-3.76 (m, 2H), 3.84 (d, J = 14.93 Hz, 1H), 4.98 (d, J = 14.93 Hz, 1H), 5.04 (d, J = 1.26 Hz, 1H), 7.22-7.26 (m, 2H), 7.28-7.41 (m, 3H), 7.51-7.66 (m, 3H), 7.73-7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.4, 35.8, 35.9, 43.9, 44.8, 51.7, 53.1, 53.9, 56.5, 98.0, 127.5, 128.1, 128.2, 129.0, 129.3, 133.0, 135.0, 136.0, 175.8; IR (thin film) 3450, 3064, 3032, 2943, 2862, 1668, 1466, 1356, 1338, 1265, 1167, 1088, 1005, 941, 924, 912, 769, 756, 731, 692, 579 cm^{-1}; LRMS (FAB, M + H): 443; HRMS Calculated for $C_{23}H_{27}N_2O_5S$ (FAB, M + H): 443.1641. Found 443.1686.



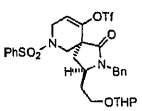
(3*R,5*S**)-2-Benzyl-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-1,10-dione (220)**. To a solution of **219** (20 g, 45.19 mmol) and DHP (4.18 g, 49.71 mmol) in CH_2Cl_2 (200 mL) was added CSA (566 mg, 2.26 mmol) at rt. After stirring for 1.5 h at ambient temperature, the reaction was quenched by addition of sat. $NaHCO_3$ (150 mL) aqueous solution and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo.

The residue was purified by flash column chromatography (silica gel, 23% to 41% EtOAc in *n*-hexane) to afford **220** as a colorless syrup (21.3 g, 90%): R_f = 0.54 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.58 (m, 10/2H), 1.60-1.78 (m, 4/2H), 1.95-2.04 (m, 2/2H), 2.08-2.17 (m, 2/2H), 2.52-2.60 (m, 4/2H), 2.79-2.91 (m, 2/2H), 2.90-2.99 (m, 2/2H), 3.31-3.42 (m, 4/2H), 3.41 (d, J = 12.29 Hz, 2/2H), 3.46-3.58 (m, 2/2H), 3.65-3.80 (m, 4/2H), 3.79 (dd, J = 12.29, 2.55 Hz, 2/2H), 3.94-4.01 (m, 2/2H), 4.06 (d, J = 15.30 Hz, 2/2H), 4.39-4.41 (m, 1/2H), 4.49-4.51 (m, 1/2H), 5.06 (d, J = 15.30 Hz, 1/2H), 5.07 (d, J = 15.30 Hz, 1/2H), 7.23-7.33 (m, 10/2H), 7.54-7.64 (m, 6/2H), 7.78-7.81 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 19.6, 25.32, 25.33, 30.5, 30.6, 33.0, 33.2, 36.96, 37.00, 37.5, 44.67, 44.70, 45.7, 52.4, 52.6, 53.7, 59.2, 62.5, 62.6, 62.9, 63.2, 98.7, 99.2, 127.5, 127.6, 127.9, 128.6, 129.4, 133.3, 135.37, 135.41, 136.2, 170.9, 203.7; IR (thin film) 2929, 2856, 1718, 1685, 1446, 1362, 1261, 1171, 1120, 1091, 1074, 1034, 999, 968, 908, 870, 800, 737, 692, 580 cm^{-1}; LRMS (FAB, M + H): 527; HRMS Calculated for $C_{28}H_{35}N_2O_6S$ (FAB, M + H): 527.2216. Found 527.2266.



Optically pure (3*S*,5*R*)-**220** was prepared as same as racemic **220**. **(3*S*,5*R*)-2-Benzyl-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diaza spiro[4.5]decane-1,10-dione [(3*S*,5*R*)-220]**: $[\alpha]_D^{20}$ –19.4° (*c* 0.32, $CHCl_3$).

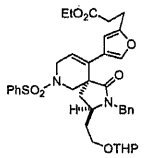
(3*R,5*S**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl] -2,7-diazaspiro[4.5]dec-9-en-10-yl Trifluoromethanesulfonate (233)**. A 1.0 M solution of lithium bis(trimethylsilyl)amide (54 mL, 54.0 mmol) in THF was added dropwise to a solution of **220** (28.18 g, 53.51 mmol) in THF (564 mL) at –78 °C for 15 min. After the solution was stirred for 45 min at the same temperature, a solution of *N*-phenylbis(trifluoromethanesulfonimide) (21.0 g, 58.86 mmol) in THF (15 mL) was introduced. Stirring was continued for additional 13 h at ambient temperature. The reaction was quenched by addition of CH_2Cl_2 (300 mL). The mixture was filtered through a pad of alumina. The pad was washed with CH_2Cl_2, and combined filtrate were concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 50% EtOAc in *n*-hexane) to afford **233** as a colorless foam (32.6 g, 92%): R_f= 0.58 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.87 (m, 14/2H), 2.11-2.21 (m, 2/2H), 2.21-2.35 (m, 2/2H), 2.42-2.52 (m, 2/2H), 3.08 (d, J = 11.81 Hz, 2/2H), 3.34 (dd, J = 16.33, 1.20 Hz, 2/2H), 3.40-3.53 (m, 4/2H), 3.65-3.88 (m, 8/2H), 4.02 (d, J = 15.00 Hz, 1/2H), 4.03 (d, J = 15.00 Hz, 1/2H), 4.23 (dd, J = 16.33, 4.21 Hz, 1/2H), 4.24 (dd, J = 16.33, 4.21 Hz, 1/2H), 4.48-4.55 (m, 2/2H), 5.04 (d, J = 15.00 Hz, 2/2H), 5.91 (dd, J = 4.21, 1.20 Hz, 2/2H), 7.22-7.32 (m, 10/2H), 7.54-7.65 (m, 6/2H), 7.75-7.79 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 19.5, 25.3,



25.4, 30.48, 30.50, 33.56, 33.63, 33.9, 34.0, 43.9, 44.95, 45.01, 50.56, 50.59, 52.3, 52.4, 53.05, 53.13, 62.3, 62.5, 63.0, 63.5, 98.5, 99.3, 113.6, 113.7, 118.3 (q, J_{CF} = 320.13 Hz), 127.5, 127.8, 128.07, 128.10, 128.71, 128.73, 129.5, 133.4, 135.19, 135.23, 135.77, 135.78, 147.70, 147.72, 169.6; IR (thin film) 2944, 2871, 1695, 1446, 1423, 1354, 1250, 1217, 1173, 1140, 1076, 1036, 970, 908, 864, 733, 692, 617, 577 cm^{-1}; LRMS (FAB, M + H): 659; HRMS Calculated for $C_{29}H_{34}N_2O_8S_2F_3$ (FAB, M + H): 659.1709. Found 659.1718.

Optically pure (3*S*,5*R*)-**233** was prepared as same as racemic **233**. **(3*S*,5*R*)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-9-en-10-yl Trifluoromethanesulfonate [(3*S*,5*R*)-233]**: $[\alpha]_D^{20}$ –54.0° (*c* 0.44, $CHCl_3$).

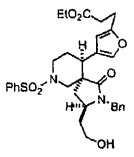
Ethyl 3-(4-[(3*R,5*R**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-9-en-10-yl]-2-furyl)propanoate (234)**. To a solution of borate **194** (3.0 g, 10.71 mmol), K_3PO_4 (4.87 g, 22.95 mmol) and triflate **233** (5.04 g, 7.65 mmol) in DMF (50 mL) was added $PdCl_2$(dppf) (280 mg, 0.38 mmol) at rt. After stirring for 3 h at 80 °C, the reaction mixture was diluted with EtOAc (300 mL). The organic layer was washed with water (100 mL, twice) and brine (100 mL), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 50% EtOAc in *n*-hexane) to afford **234** as slight yellow syrup (4.90 g, 95%): R_f = 0.44 (silica gel, EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.13 Hz, 6/2H), 1.45-1.81 (m, 14/2H), 2.18-2.27 (m, 4/2H), 2.30-2.37 (m, 2/2H), 2.58 (t, J = 7.91 Hz, 4/2H), 2.85 (t, J = 7.91 Hz, 4/2H), 2.91 (d, J = 11.61 Hz, 1/2H), 2.92 (d, J = 11.61 Hz, 1/2H), 3.25 (dd, J = 14.66, 2.05 Hz, 2/2H), 3.44-3.64 (m, 6/2H), 3.74 (brd, J = 11.61 Hz, 2/2H), 3.72-3.91 (m, 4/2H), 4.04 (d, J = 14.08 Hz, 2/2H), 4.01-4.10 (m, 2/2H), 4.14 (q, J = 7.13 Hz, 4/2H), 4.55 (brm, 2/2H), 4.98 (d, J = 14.08 Hz, 2/2H), 5.82 (dd, J = 2.85, 1.79 Hz, 2/2H), 5.94 (s, 2/2H), 6.91 (s, 1/2H), 6.93 (s, 1/2H), 7.21-7.37 (m, 10/2H), 7.52-7.65 (m, 6/2H), 7.72-7.79 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.5, 19.6, 23.3, 25.3, 25.4, 30.6, 30.6, 32.5, 33.5, 33.6, 34.2, 34.3, 44.6, 44.7, 45.2, 50.1, 52.2, 52.3, 52.4, 52.5, 60.5, 62.3, 62.5, 63.3, 63.8, 98.6, 99.3, 105.5, 105.6, 121.5, 123.7, 127.5, 127.8, 128.6, 128.7, 128.7, 128.8, 129.2, 131.6, 133.0, 135.5, 135.8, 137.9, 154.4, 172.2, 173.4; IR (thin film) 2943, 2871, 1732, 1685, 1446, 1352, 1254, 1167, 1034, 974, 910, 729, 704, 692, 609, 575; LRMS (FAB, M + H): 677; HRMS Calculated for $C_{37}H_{45}N_2O_8S$ (FAB, M + H): 677.2897. Found 677.2919; Anal. Calculated for $C_{37}H_{44}N_2O_8S$ C: 65.66, H: 6.55, N: 4.14, O: 18.91, S: 4.74. Found C: 65.38, H: 6.73, N: 3.90.



Optically pure (3*S*,5*S*)-234 was prepared as same as racemic **234**. Ethyl 3-(4-[(3*S*,5*S*)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-9-en-10-yl]-2-furyl)propanoate [(3*S*,5*S*)-234]: $[\alpha]_D^{20}$ −115.7° (*c* 0.29, $CHCl_3$).

Ethyl 3-(4-[(3*R**,5*R**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate (**236**), Ethyl 3-(4-[(3*R**,5*R**,10*S**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-(2-hydroxyethyl)-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate [(3*R**,5*R**,10*S**)-237] and Ethyl 3-(4-[(3*R**,5*R**,10*R**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-(2-hydroxyethyl)-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate [(3*R**,5*R**,10*R**)-237]. To a degassed solution of **234** (4.87 g, 7.20 mmol) in MeOH (130 mL) was added Pd on charcoal (4.8 g, 10% Pd) at rt. The resulting slurry was hydrogenated over 1.5 h and filtered. The charcoal was washed with EtOAc (130 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, 16% to 50% EtOAc in *n*-hexane) to afford **236** as a colorless syrup (4.12 g, 92%, H-8 α:β 76:24). To a solution of **236** (4.12 g, 6.07 mmol, H-8 α:β 76:24) in EtOH (80 mL) was added PPTS (305 mg, 1.21 mmol) at rt. After stirring for 3 h at 50 °C, a reaction was quenched by addition of sat. $NaHCO_3$ aqueous solution and concentrated in vacuo. The residue was dissolved in EtOAc (120 mL), and the solution was washed with water (70 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 37% to 67% EtOAc in *n*-hexane) to afford affording (3*R**,5*R**,10*S**)-**237** (2.58 g, 72%) and as a syrup (3*R**,5*R**,10*R**)-237 (0.81 g, 22%).

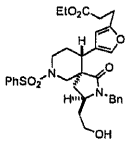
Ethyl 3-(4-[(3*R**,5*R**,10*S**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-(2-hydroxyethyl)-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate [(3*R**,5*R**,10*S**)-237]: R_f = 0.20 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.13 Hz, 3H), 1.31-1.43 (m, 1H), 1.51 (dd, J = 13.65, 5.61 Hz, 1H), 1.61-1.67 (m, 1H), 1.92-2.03 (m, 1H), 2.18 (dd, J = 13.65, 8.35 Hz, 1H), 2.34 (dd, J = 11.90, 4.69 Hz, 1H), 2.50-2.59 (m, 2H), 2.53 (t, J = 7.20 Hz, 2H), 2.70-2.83 (m, 1H), 2.83 (t, J = 7.20 Hz, 2H), 3.05-3.14 (m, 1H), 3.53-3.59 (m, 3H), 3.71-3.76 (m, 1H), 3.88 (d, J = 12.04 Hz, 1H), 4.05 (d, J = 15.21 Hz, 1H), 4.12 (dq, J = 7.13, 1.59 Hz, 2H), 4.63 (d, J = 15.21 Hz, 1H), 5.90 (s, 1H), 6.99-7.03 (m, 2H), 7.10 (s, 1H), 7.19-7.30 (m, 3H), 7.50-7.60 (m, 3H), 7.86-7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.4, 27.7, 32.5, 36.5, 36.9, 40.5, 44.4, 45.65, 45.68, 52.0, 53.7, 58.9, 60.5, 106.6, 124.7, 127.1, 127.8 (2C), 128.4, 128.9, 132.6, 136.5,



136.8, 138.7, 154.3, 172.4, 174.0; IR (thin film) 3450, 2929, 2873, 1732, 1672, 1446, 1336, 1255, 1167, 1095, 1053, 1034, 972, 912, 817, 735, 692, 584 cm^{-1}; LRMS (FAB, M + H) 595; HRMS Calculated for $C_{32}H_{39}N_2O_7S$ (FAB, M + H) 595.2477. Found 595.2488.

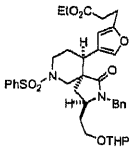
Optically pure (3*S*,5*S*,10*R*)-**237** was prepared as same as racemic **237**. **Ethyl 3-(4-[(3*S*,5*S*,10*R*)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-(2-hydroxyethyl)-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate** [(3*S*,5*S*,10*R*)-**237**]. $[\alpha]_D^{20}$ –3.2° (*c* 0.34, $CHCl_3$).

Ethyl 3-(4-[(3*R,5*R**,10*R**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-(2-hydroxyethyl)-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate** [(H-8β)-**237**]: R_f = 0.35 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.14 Hz, 3H), 1.46-1.58 (m, 1H), 1.71-1.74 (brs, 1H), 1.78-1.94 (m, 2H), 1.95-2.06 (m, 1H), 2.01 (dd, J = 13.94, 4.75 Hz, 1H), 2.15 (dd, J = 13.94, 8.91 Hz, 1H), 2.32-2.41 (m, 1H), 2.54 (t, J = 7.83 Hz, 2H), 2.64 (d, J = 11.61 Hz, 1H), 2.84 (t, J = 7.83 Hz, 2H), 2.88 (dd, J = 11.70, 5.61 Hz, 1H), 3.08-3.17 (m, 1H), 3.61-3.67 (m, 2H), 3.63 (dd, J = 11.61, 1.83 Hz, 1H), 3.89-3.93 (m, 1H), 4.03 (d, J = 15.15 Hz, 1H), 4.06-4.16 (m, 2H), 4.79 (d, J = 15.15 Hz, 1H), 5.85 (s, 1H), 6.96-7.00 (m, 2H), 7.05 (s, 1H), 7.22-7.27 (m, 3H), 7.54-7.62 (m, 3H), 7.73-7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.5 26.9, 29.5, 32.6, 36.5, 37.2, 44.5, 46.4, 49.7, 52.6, 54.9, 59.0, 60.6, 106.1, 124.7, 127.4, 127.8, 128.5, 129.2, 133.0, 135.8, 136.1, 138.6, 154.6, 172.4, 174.9; IR (thin film) 3450, 2931, 2856, 1732, 1674, 1446, 1354, 1336, 1261, 1163, 1097, 1034, 974, 912, 804, 735, 692, 580, 548 cm^{-1}; LRMS (FAB, M + H) 595; HRMS Calculated for $C_{32}H_{39}N_2O_7S$ (FAB, M + H) 595.2477. Found 595.2475.



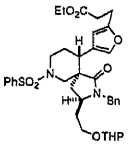
Ethyl 3-(4-[(3*R,5*R**,10*S**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate (236).** To a solution of (3*R**,5*R**,10*S**)-**237** (11.45 g, 19.25 mmol) and DHP (1.78 g, 21.18 mmol) in CH_2Cl_2 (171 mL) was added CSA (241mg, 0.96 mmol) at rt. After stirring for 1.5 h at ambient temperature, the reaction was quenched by addition of sat. $NaHCO_3$ (150 mL) aqueous solution and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5% to 80% EtOAc in *n*-hexane) to afford **236** as a colorless syrup (12.6 g, 96%): R_f = 0.45 (silica gel, EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.14 Hz, 6/2H), 1.31-1.88 (m, 14/2H), 1.62-1.66 (m, 2/2H), 1.98-2.10 (m, 2/2H), 2.16 (dd, J = 13.46, 8.41 Hz, 2/2H), 2.36 (dd, J = 11.88, 3.63 Hz, 2/2H), 2.53 (t, J = 7.18 Hz, 4/2H), 2.56-2.65 (m, 4/2H), 2.76 (m, 2/2H), 2.82 (t, J = 7.18 Hz, 2/2H), 2.83 (t,

J = 7.18 Hz, 2/2H), 3.07-3.09 (m, 2/2H), 3.24-3.48 (m, 4/2H), 3.57-3.66 (m, 6/2H), 3.88 (d, J = 12.08 Hz, 2/2H), 3.90-4.09 (m, 2/2H), 4.13 (q, J = 7.14 Hz, 4/2H), 4.41-4.47 (m, 2/2H), 4.66 (d, J = 15.17 Hz, 1/2H), 4.68 (d, J = 15.17 Hz, 1/2H), 5.90 (s, 1H), 7.01-7.50 (m, 2H), 7.10 (s, 1H), 7.20-7.27 (m, 3H), 7.52-7.60 (m, 3H), 7.89-7.92 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 14.2, 19.5, 19.5, 23.4, 25.3, 27.8, 30.6, 32.5, 34.1, 34.3, 36.5, 36.6, 40.5, 40.6, 44.3, 44.4, 45.6, 45.6, 49.6, 52.1, 52.2, 53.6, 60.5, 62.4, 62.4, 63.3, 63.8, 98.6, 99.1, 106.5, 106.5, 124.8, 127.2, 127.9, 127.9, 128.5, 128.4, 132.6, 136.6, 137.1, 137.1, 138.7, 154.4, 154.4, 172.3, 174.8, 174.9; IR (thin film) 2941, 2870, 1732, 1682, 1446, 1352, 1338, 1257, 1169, 1120, 1095, 1076, 1034, 974, 906, 870, 814, 735, 692, 582 cm^{-1}; LRMS (FAB, M + H): 679; HRMS Calculated for $C_{37}H_{47}N_2O_8S$ (FAB, M + H): 679.3053. Found 679.3074.

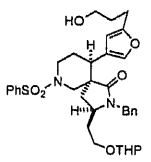


Optically pure (3*S*,5*S*,10*R*)-**236** was prepared as same as racemic **236**. **Ethyl 3-(4-[(3*S*,5*S*,10*R*)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy) ethyl]-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate [(3*S*,5*S*,10*R*)-236]**: $[\alpha]_D^{20}$ +3.8° (*c* 0.24, $CHCl_3$); Anal. Calculated for $C_{32}H_{38}N_2O_7S$. 1/2 H_2O, C: 65.09, H: 7.02, N: 4.34, O: 18.58, S: 4.97. Found C: 65.08, H: 6.93, N: 4.13.

Pure (3*R**,5*R**,10*R**)-**236** was prepared as same as (3*R**,5*R**,10*S**)-**236**. **Ethyl 3-(4-[(3*R**,5*R**,10*R**)-2-Benzyl-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yl oxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl]-2-furyl)propanoate [(H-8β)-236]**: R_f= 0.49 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.14 Hz, 6/2H), 1.40-2.19 (m, 48/2H), 2.30-2.41 (m, 2/2H), 2.51 (t, J = 8.22 Hz, 4/2H), 2.64 (d, J = 11.66 Hz, 2/2H), 2.82 (t, J = 8.22 Hz, 4/2H), 2.79-2.90 (m, 2/2H), 3.07-3.12 (m, 2/2H), 3.35-3.51 (m, 4/2H), 3.59-3.65 (m, 2/2H), 3.66-3.81 (m, 4/2H), 3.99-3.92 (m, 2/2H), 4.02 (d, J = 15.02 Hz, 1/2H), 4.04 (d, J = 15.02 Hz, 1/2H), 4.13 (q, J = 7.14 Hz, 4/2H), 4.47-4.49 (m, 1/2H), 4.51-4.53 (m, 1/2H), 4.79 (d, J = 15.02 Hz, 1/2H), 5.82 (s, 2/2H), 6.99-7.04 (m, 4/2H), 7.04(s, 1/2H), 7.05 (s, 1/2H), 7.22-7.26 (m, 6/2H), 7.54-7.62 (m, 6/2H), 7.73-7.76 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 19.57, 19.58, 23.5, 25.4, 26.9, 29.79, 29.87, 30.58, 30.61, 32.6, 33.8, 33.9, 37.3, 44.4, 44.5, 46.4, 49.6, 52.6, 52.7, 54.9, 55.0, 60.5, 62.4, 62.5, 63.2, 63.7, 98.6, 99.2, 106.1, 124.8, 127.4, 127.5, 127.9, 128.0, 128.45, 128.47, 129.2, 132.9, 135.84, 135.87, 136.1, 138.5, 154.6, 172.3, 174.9, 174.9; IR (thin film) 2941, 2871 ,2854, 1732, 1682, 1446, 1373, 1354, 1338, 1261, 1171, 1122, 1097, 1074, 1034, 974, 904, 812, 735, 692, 582, 494 cm^{-1}; LRMS (FAB, M + H): 679; HRMS Calculated for $C_{37}H_{47}N_2O_8S$ (FAB, M + H): 679.3053. Found 679.3000; Anal. Calculated for $C_{32}H_{38}N_2O_7S$. 1/2 H_2O, C: 65.09, H: 7.02, N: 4.34, O: 18.58, S: 4.97. Found C: 65.08, H: 6.93, N: 4.13.



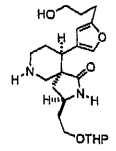
(3*R,5*R**,10*S**)-2-Benzyl-10-[5-(3-hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decan-1-one (246).** To a solution of ethyl ester **236** (17.67 g, 26.03 mmol) in THF (350 mL) and MeOH (7.43 g, 0.23 mol) was slowly added $LiBH_4$ (1.25 g, 57.27 mmol) at 3 °C. After stirring for 1 h at 3 °C, the reaction mixture was stirred for 18 h at rt. The mixture was quenched by addition of water (100 mL) and concentrated in vacuo. The residue was dissolved in EtOAc (350 mL) and water (50 mL), and the mixture was acidified to pH 5 with 1 *N* HCl (60 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (100 mL) aqueous solution and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 11% to 35% EtOAc in *n*-hexane) to afford alcohol **246** as a colorless foam (15.52 g, 94%): R_f = 0.21 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.80 (m, 18/2H), 1.80-1.86 (m, 4/2H), 1.91-2.08 (m, 2/2H), 2.18 (dd, J = 13.48, 7.67 Hz, 2/2H), 2.37 (dd, J = 11.67, 3.85 Hz, 2/2H), 2.58-2.67 (m, 6/2H), 2.62 (t, J = 7.15 Hz, 4/2H), 2.72-2.91 (m, 2/2H), 3.03-3.15 (m, 2/2H), 3.22-3.75 (m, 10/2H), 3.61 (t, J = 6.34 Hz, 4/2H), 3.88 (d, J = 12.15 Hz, 2/2H), 4.07 (dd, J = 15.19, 3.99 Hz, 2/2H), 4.41-4.43 (m, 1/2H), 4.46-4.48 (m, 1/2H), 4.66 (dd, J = 15.19, 2.50 Hz, 2/2H), 5.90 (s, 2/2H), 7.01-7.05 (m, 4/2H), 7.10 (s, 2/2H), 7.19-7.27 (m, 6/2H), 7.51-7.62 (m, 6/2H), 7.89-7.94 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.58, 19.63, 24.4, 25.3, 27.9, 30.6, 30.9, 34.2, 34.4, 36.71, 36.78, 40.5, ,40.6, 44.4, 44.5, 45.66, 45.72, 52.2, 52.4, 53.6, 61.9, 62.6, 63.4, 63.9, 98.8, 99.3, 106.4, 124.8, 127.2, 127.9 (2C), 128.4, 128.9, 132.6, 136.6, 137.1, 138.4, 155.9, 174.0; IR (thin film) 3400, 2941, 2870, 1678, 1446, 1352, 1163, 1120, 1074, 1034, 972, 904, 814, 746, 692, 582 cm^{-1}; LRMS (FAB, M + H): 637; HRMS Calculated for $C_{35}H_{45}N_2O_7S$ (FAB, M + H): 637.2947. Found 637.2963; Anal. Calculated for $C_{35}H_{44}N_2O_7S$. 1/2 H_2O C: 65.09, H: 7.02, N: 4.34, O: 18.58, S: 4.97. Found C: 65.01, H: 7.03, N: 4.35.



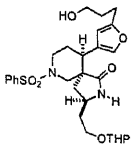
Optically pure **(3*S*,5*S*,10*R*)-246** was prepared as same as racemic **246**. **(3*S*,5*S*,10*R*)-2-Benzyl-10-[5-(3-hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decan-1-one** [**(3*S*,5*S*,10*R*)-246**]: $[\alpha]_D^{20}$ +3.1° (*c* 0.20, $CHCl_3$).

(3*R,5*R**,10*S**)-10-[5-(3-Hydroxypropyl)-3-furyl]-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decan-1-one (E-2)** and **(3*R**,5*R**,10*S**)-10-[5-(3-Hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decan-1-one (247).** To a solution of THF (50 mL) and liq. NH_3 (250 mL) was slowly added Lithium thin plates (1.5 g, 0.22 mol) at –78 °C

in a stream of nitrogen. After mechanical stirring, the color of the mixture turned blue. The solution of **246** (8.29 g, 13.02 mmol) in THF (150 mL) was added dropwise over 30 min to maintain a blue color persisted. After stirring for 30 min at –78 °C, the reaction was quenched by addition of powdered NH_4Cl (16 g) at –78 °C. After the disappearance of blue color of the mixture, NH_3 and solvent were removed and the residue was extracted with EtOAc (500 mL). Combined organic layers were washed with 1 *N*NaOH (50 mL, three times) aqueous solution, water (50 mL) and brine (50 mL), concentrated in vacuo without drying to give the residue. A small amount of **E-2** was separated by preparative TLC. R_f= 0.07 (silica gel, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-1.37 (m, 2/2H), 1.48-1.92 (m, 22/2H), 2.00-2.19 (m, 2/2H), 2.21-2.37 (m, 2/2H), 2.55 (dd, J = 12.78, 3.56 Hz, 2/2H), 2.58-2.75 (m, 8/2H), 2.78-2.96 (m, 2/2H), 3.11 (dd, J = 13.81, 3.31 Hz, 2/2H), 3.13-3.24 (m, 2/2H), 3.27-3.81 (m, 12/2H), 4.42-4.49 (m, 2/2H), 6.05 (s, 2/2H), 6.14 (brs, 1/2H), 6.19 (brs, 1/2H), 7.18(s, 2/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 20.3, 24.3, 24.4, 25.2, 25.3, 29.8, 30.3, 30.6, 30.8, 30.9, 36.9, 37.2, 40.6, 40.8, 42.10, 42.12, 44.5, 44.7, 46.5, 50.7, 51.5, 56.3, 56.5, 61.2, 61.5, 62.6, 63.6, 65.6, 66.8, 99.2, 100.1, 105.8126.3, 126.3, 137.5, 137.6, 156.0, 179.7, 179.8; IR (thin film) 3408, 3300, 1678, 1439, 1122, 1074, 1032 cm^{-1}; LRMS (FAB, M + H): 407; HRMS Calculated for $C_{22}H_{35}N_2O_5$ (FAB, M + H): 407.2546. Found 407.2592.



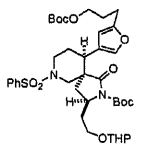
The residue was diluted with EtOAc (100 mL) and stirred with aq. $NaHCO_3$ (1.75 g, 20.9 mmol) in water (20 mL). To this mixture was added dropwise benzenesulfonyl chloride (2.58 g, 14.61 mmol) at 0 °C. After vigorous stirring for 1 h at rt, the aqueous layer was extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 16% to 65% EtOAc in *n*-hexane) to afford alcohol **247** as a colorless amorphous solid (5.71 g, 80%): R_f= 0.13 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.87 (m, 20/2H), 1.81-1.87 (m, 4/2H), 2.09-2.21 (m, 4/2H), 2.36-2.41 (m, 2/2H), 2.49-2.67 (m, 4/2H), 2.65 (t, J = 7.09 Hz, 4/2H), 2.94-3.09 (m, 2/2H), 3.31-3.86 (m, 16/2H), 4.44-4.46 (m, 1/2H), 4.49-4.51 (m, 1/2H), 6.01 (s, 1/2H), 6.18(s, 1/2H), 6.16 (brs, 1/2H), 6.18(brs, 1/2H), 7.15 (s, 2/2H), 7.50-7.60 (m, 6/2H), 7.87-7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 20.3, 24.25, 24.29, 25.18, 25.23, 28.0, 30.3, 30.6, 30.7, 30.8, 36.8, 37.1, 40.4, 40.76, 40.8, 41.1, 45.0, 45.1, 45.48, 45.54, 49.8, 50.5, 52.5, 52.6, 61.3, 61.5, 62.6, 63.5, 65.4, 66.4, 99.2, 100.0, 106.0, 106.1, 124.75, 124.76, 127.8, 128.9, 128.9, 132.6, 136.9, 137.0, 137.9, 138.0, 156.0, 156.1, 176.4, 176.5; IR (thin film) 3415, 2941, 2871, 1691, 1446, 1336, 1163, 1122, 1074, 1032, 976, 906, 812, 773, 731, 692, 582 cm^{-1}; LRMS (FAB, M + H): 547; HRMS Calculated for $C_{28}H_{39}N_2O_7S$ (FAB, M + H): 547.2478. Found



547.2440; Anal. Calculated for $C_{28}H_{38}N_2O_7S$. 1/2 H_2O, C: 60.52, H: 7.07, N: 5.04, O: 21.59, S: 5.77. Found C: 60.27, H: 7.17, N: 4.81.

Optically pure (3*S*,5*S*,10*R*)-**247** was prepared as same as racemic **247**. **(3*S*,5*S*,10*R*)-10-[5-(3-Hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decan-1-one [(3*S*,5*S*,10*R*)-247]**: $[\alpha]_D^{20}$ –8.5° (*c* 0.20, $CHCl_3$).

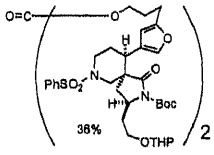
***tert*-Butyl (3*R**,5*R**,10*S**)-10-(5-[3-[(*tert*-Butoxycarbonyl)oxy]propyl]-3-furyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate (248) and Bis [3-[4-((3*R**,5*R**,10*S**)-2-(*tert*-Butoxycarbonyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl)-2-furyl]propyl] Carbonate (249).** To a solution of amide **247** (7.3 g, 13.35 mmol), DMAP (163 mg, 1.34 mmol) and Et_3N (4.05 g, 40.06 mmol) in THF (146 mL) was added di-*tert*-butyldicarbonate (8.74 g, 40.06 mmol) at 0 °C. After stirring for 11 h at rt, the reaction mixture was concentrated in vacuo and extracted with EtOAc. Combined organic layers were washed with 0.5 *N* HCl (100 mL, twice) aqueous solution, sat. $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 20% EtOAc in *n*-hexane) to afford nomomer **248** (6.82 g, 68%) and dimeric carbonate **249** (2.66 g, 30%). ***tert*-Butyl (3*R**,5*R**,10*S**)-10-(5-[3-[(*tert*-Butoxycarbonyl)oxy]propyl]-3-furyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate (248)**: R_f = 0.64 (silica gel, EtOAc/*n*-hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.80 (m, 20/2H), 1.48 (s, 18/2H), 1.50 (s, 18/2H), 1.81-1.97 (m, 4/2H), 2.03-2.28 (m, 4/2H), 2.30-2.41 (m, 2/2H), 2.50-2.64 (m, 8/2H), 3.33-3.43 (m, 2/2H), 3.48-3.63 (m, 4/2H), 3.68-3.89 (m, 6/2H), 3.98 (d, J = 11.84 Hz, 2/2H), 4.05 (t, J = 6.47 Hz, 4/2H), 4.52-4.55 (m, 2/2H), 5.87 (s, 2/2H), 7.10 (s, 2/2H), 7.51-7.62 (m, 6/2H), 7.88-7.92 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.5, 25.4, 27.2, 27.8, 28.1, 29.7, 30.61, 30.64, 35.1, 35.3, 35.4, 35.5, 41.6, 41.7, 45.7, 46.6, 46.6, 52.25, 52.32, 52.7, 52.9, 62.4, 62.4, 63.8, 64.0, 66.0, 81.9, 82.7, 98.8, 99.0, 105.8, 124.3, 128.0, 129.0, 132.7, 136.9, 138.4, 149.9, 153.5, 155.7, 173.4, 173.4; IR (thin film) 2976, 2937, 2854, 1778, 1738, 1354, 1281, 1255, 1159, 1034, 744, 582 cm^{-1}; LRMS (FAB, M + Na): 769; HRMS Calculated for $C_{38}H_{54}N_2O_{11}S$ (FAB, M + Na): 769.3346. Found 769.3325; Anal. Calcd for $C_{38}H_{54}N_2O_{11}S$ C: 61.11, H: 7.29, N: 3.75, O: 23.56, S: 4.29. Found C: 60.89, H: 7.35, N: 3.65.



Optically pure (3*S*,5*S*,10*R*)-**248** was prepared as same as racemic **248**. ***tert*-Butyl**

(3*S*,5*S*,10*R*)-10-(5-[3-[(*tert*-Butoxycarbonyl)oxy]propyl]-3-furyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate [(3*S*,5*S*,10*R*)-248]: $[\alpha]_D^{20}$ –60.0° (*c* 0.36, $CHCl_3$).

Bis [3-[4-((3*R**,5*R**,10*S**)-2-(*tert*-Butoxycarbonyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl)-2-furyl]propyl] Carbonate (249): R_f = 0.36 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38-1.88 (m, 22H), 1.50(s, 18H), 1.89-1.99 (m, 4H), 2.03-2.26 (m, 4H), 2.31-2.36 (m, 2H), 2.47-2.56 (m, 6H), 2.60 (t, 4H), 3.34-3.84 (m, 12H), 3.98 (d, 2H), 4.14 (t, 4H), 4.53 (s, 2H), 5.86 (s, 2H), 7.11 (s, 2H), 7.52-7.63 (m, 6H), 7.83-7.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 24.2, 25.2, 26.9, 27.6, 27.8, 30.40, 30.42, 34.9, 35.1, 35.2, 35.3, 41.3, 41.4, 45.5, 46.27, 46.28, 52.1, 52.2, 52.5, 52.7, 62.1, 62.2, 63.6, 63.8, 66.7, 82.4, 98.6, 98.8, 105.6, 124.1, 127.7, 128.8, 132.6, 136.6, 138.3, ,150.0, 155.3, 173.18, 173.23; IR (thin film) 2941, 2871, 1776, 1741, 1716, 1446, 1354, 1259, 1157, 1034, 972, 906, 791, 733, 692, 582 cm^{-1}; LRMS (FAB, M + Na): 1341; HRMS Calculated for $C_{67}H_{90}N_4O_9S_2$ (FAB, M + Na): 1341.5538. Found 1341.5538; Anal. Calculated for $C_{67}H_{90}N_4O_{19}S_2$ C: 60.98, H: 6.87, N: 4.25, O: 23.04, S: 4.86. Found C: 60.61, H: 6.96, N: 4.08.



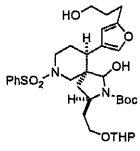
Optically pure (3*S*,5*S*,10*R*)-249 was prepared as same as racemic 249. Bis[3-[4-((3*S*,5*S*,10*R*)-2-(*tert*-Butoxycarbonyl)-1-oxo-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]dec-10-yl)-2-furyl]propyl] Carbonate [(3*S*,5*S*,10*R*)-249]: $[\alpha]_D^{20}$ –43.9° (*c* 0.23, $CHCl_3$).

tert-Butyl (3*R**,5*R**,10*S**)-1-Hydroxy-10-[5-(3-hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate (E-3) and *tert*-Butyl (3*R**,5*R**,10*S**)-1-(Acetyloxy)-10-[5-[3-(acetyloxy)propyl]-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate (250). A 1.5 M solution of DIBAL-H in toluene (7.2 mL, 10.75 mmol) was added dropwise to a solution of dimer 249 (2.58 g, 1.96 mmol) in toluene (26 mL) and CH_2Cl_2 (26 mL) at –78 °C. The mixture was warmed to 0 °C over 2 h and stirring was continued for 1 h at rt. After the solution was cooled to –78 °C, 0.7 M Rochelle's salt (5 mL) was added dropwise and then the mixture was warmed to 0 °C over 1 h and stirred for 1 h at rt. After EtOAc (100 mL) and 0.7 M Rochelle's salt (40 mL) were added, separated organic layer was washed with 0.7 M Rochelle's salt (40 mL, three times) and brine (55 mL), dried over

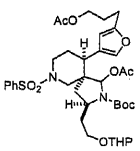
$MgSO_4$ and concentrated in vacuo to give a residue (**E-3**).

A 1.5 M solution of DIBAL-H in toluene (26.4 mL, 39.6 mmol) was added dropwise to a solution of carbamate **248** (6.72 g, 9.00 mmol) in toluene (67 mL) and CH_2Cl_2 (67 mL) at −78 °C. The mixture was warmed to 0 °C over 2 h and stirring was continued for 1 h at rt. After the solution was cooled to −78 °C, 0.7 M Rochelle's salt (15 mL) was added dropwise and then the mixture was warmed to 0 °C over 1 h and stirred for 1 h at rt. After EtOAc (300 mL) and 0.7 M Rochelle's salt (110 mL) were added, separated organic layer was washed with 0.7 M Rochelle's salt (110 mL, three times) and brine (165 mL), dried over $MgSO_4$ and concentrated in vacuo to give a residue (**E-3**).

Combined residue was dissolved in pyridine (15 mL) and acetic anhydride (15 mL). After the mixture was stirred for 12 h at rt, EtOAc (500 mL) and 1 *N* HCl (150 mL, three times) were added. Separated organic layer was washed with sat. $NaHCO_3$ (100 mL, three times) aqueous solution and brine (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 10% to 30% EtOAc in *n*-hexane) to afford acetate **250** as a colorless syrup (7.57 g, 80.0% from carbamate **248** and **249**). ***tert*-Butyl (3*R**,5*R**,10*S**)-1-Hydroxy-10-[5-(3-hydroxypropyl)-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate** (**E-3**): R_f = 0.25 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-2.15 (m, 78/6H), 2.29-2.66 (m, 30/6H), 1.48 (s, 54/6H), 2.57 (t, J = 7.43 Hz, 12/6H), 2.89 (brs, 6/6H), 3.10-3.16 (m, 5/6H), 3.15-3.62 (m, 20/6H), 3.60 (t, J = 6.29 Hz, 12/6H), 3.77-4.00 (m, 23/6H), 4.52 (m, 1/6H), 4.64-4.65 (m, 5/6H), 4.74 (s, 1/6H), 4.91 (s, 5/6H), 5.72 (s, 5/6H), 5.80 (s, 1/6H), 6.80 (s, 5/6H), 6.94 (s, 1/6H), 7.54-7.67 (m, 18/6H), 7.76-7.79 (m, 12/6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 24.2, 25.5, 27.6, 28.4, 30.6, 30.7, 35.0, 35.2, 35.8, 36.1, 36.5, 42.6, 48.12 (2C), 54.7, 55.3, 61.9, 62.2, 65.1, 65.5, 80.9, 85.7, 85.8, 98.2, 98.4, 108.0, 125.3, 125.5, 127.7, 127.7, 129.1, 132.9, 135.6, 137.8, 154.9, 156.2; IR (thin film) 3450, 2941, 2871, 1684, 1387, 1354, 1336, 1167, 1034, 953, 744, 692, 579 cm^{-1}; LRMS (FAB, M + Na): 671; HRMS Calculated for $C_{33}H_{48}N_2O_9S$ (FAB, M + Na): 671.2978. Found 671.2990.

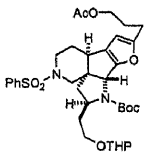


***tert*-Butyl (3*R**,5*R**,10*S**)-1-(Acetyloxy)-10-[5-[3-(acetyloxy)propyl]-3-furyl]-7-(phenylsulfonyl)-3-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-2,7-diazaspiro[4.5]decane-2-carboxylate** (**250**): R_f = 0.69 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-2.20 (m, 96/8H), 1.41 (s, 45/8H), 1.48 (s, 27/8H), 1.79(24/8H, s), 2.04(s, 24/8H), 2.20-2.95 (m, 24/8H), 2.54 (t, J = 7.22 Hz, 16/8H,), 3.05-4.10 (m, 72/8H), 4.04 (t, J = 6.50 Hz, 16/8H), 4.55 (brs, 1/8H), 4.66 (brs, 7/8H), 4.91 (s, 1/8H), 5.24 (s, 2/8H), 5.55 (s, 5/8H), 5.73-5.78 (m, 3/8H), 6.15 (s, 5/8H), 6.73 (s, 5/8H), 6.79 (s, 3/8H),



7.52-7.69 (m, 24/8H), 7.76-7.81 (m, 16/8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 19.5, 20.9, 24.2, 24.3, 25.5, 26.8, 26.9, 28.3, 28.4, 30.7, 30.7, 34.8, 36.8, 42.3, 49.1, 55.4, 56.2, 61.9, 62.1, 62.2, 63.5, 65.2, 65.6, 80.86, 80.95, 80.99, 84.8, 84.9, 98.4, 107.3, 124.6, 127.7, 127.7, 129.1, 129.2, 132.9, 133.0, 137.4, 137.9, 154.1, 154.66, 167.8, 171.0; IR (thin film): 2941, 2870, 1738, 1705, 1446, 1367, 1338, 1242, 1169, 1036, 957, 904, 742, 692, 579 cm^{-1}; LRMS (FAB, M + Na) 755; HRMS Calculated for $C_{37}H_{52}N_2O_{11}S$ (FAB, M + Na): 755.3190. Found 755.3204.

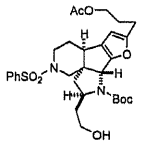
tert-Butyl (2*R**,3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl}-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (251). To a solution of acetate **250** (7.47 g, 10.19 mmol) in CH_2Cl_2 (130 mL) was added *p*-TsOH monohydrate (1.94 g, 10.19 mmol) at rt. After stirring for 1.2 h at rt, the reaction was quenched by addition of sat. $NaHCO_3$ (100 mL) aqueous solution and extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ (100 mL) aqueous solution and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 90% EtOAc in *n*-hexane) to afford **251** (2.96 g, 43%) and **252** (2.22 g, 37%) as a colorless syrup. *tert*-Butyl (2*R**,3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl}-5-(phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate (251): R_f = 0.70 (silica gel, EtOAc/*n*-hexane, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-1.82 (m, 16/2H), 1.53(s, 18/2H), 1.90-2.12(m, 2/2H), 1.90-2.00 (m, 4/2H), 2.04 (s, 6/2H), 2.40-2.55 (brm, 2/2H), 2.61-2.68 (m, 2/2H), 2.66 (t, J = 7.56 Hz, 4/2H), 2.95-3.25 (brm, 6/2H), 3.40-3.70 (brm, 6/2H), 3.70-4.00 (m, 6/2H), 4.09 (t, J = 6.41 Hz, 4/2H), 4.50-4.58 (m, 2/2H), 4.69 (s, 1H), 5.78 (s, 2/2H), 7.50-7.63 (m, 6/2H), 7.77-7.80 (m, 4/2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 19.6, 20.9, 25.4, 25.5, 27.0, 27.9, 28.0, 28.4, 30.7, 35.0, 39.8, 41.6, 41.8, 42.2, 42.3, 50.6, 56.1, 56.3, 58.5, 62.2, 63.06, 63.12, 63.5, 65.1, 65.4, 79.77, 79.80, 98.7, 98.9, 102.7, 127.3, 128.7, 129.1, 132.7, 137.45, 137.47, 154.5, 155.6, 159.9, 171.0; IR (thin film) 2941, 2871, 1738, ,1693, 1446, 1389, 1354, 1244, 1167, 1136, 1074, 1034, 982, 910, 739, 692, 582 cm^{-1}; LRMS (FAB, M + Na): 695; HRMS Calculated for $C_{35}H_{48}N_2O_9S$ (FAB, M + Na): 695.2978. Found 695.3011; Anal. Calculated for $C_{35}H_{48}N_2O_9S$ C: 62.48, H: 7.19, N: 4.16, O: 21.40, S: 4.77. Found C: 62.26, H: 7.34, N: 4.14.

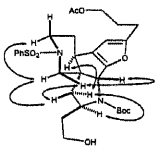


Optically pure (*S*)-**251** was prepared as same as racemic **251**. *tert*-Butyl (2*S*,3a*S*,7a*S*,10b*S*)-9-[3-(Acetyloxy)propyl]-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl}-5-(

phenylsulfonyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopent a[1,2-c]pyridine-1-carboxylate [(*S*)-**251**]: $[\alpha]_D^{20}$ –34.3° (*c* 0.27, $CHCl_3$).

tert-Butyl (2*R**,3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-2-(2-hydroxyethyl)-5-(phenylsulfonyl)-2 ,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1 -carboxylate (**252**). To a solution of **251** (2.86 g, 4.25 mmol) in THF (100 mL) was added and stirred 1 *N* HCl (100 mL) aqueous solution at rt. After stirring for 0.5 h at rt, the reaction was quenched by addition of sat. $NaHCO_3$ (80 mL) aqueous solution and concentrated in vacuo. The residue was dissolved in EtOAc (300 mL) and combined extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 90% EtOAc in *n*-hexane) to afford **252** as a colorless syrup (2.04 g, 82%): R_f = 0.29 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45-1.60 (m, 2H), 1.55 (s, 9H), 1.74-1.85 (m, 1H), 1.85-2.06 (m, 2H), 1.89-1.98 (m, 2H), 2.04 (s, 3H), 2.18 (dd, J = 13.48, 9.00 Hz, 1H), 2.59 (t like, J = 6.52 Hz, 1H), 2.66 (t, J = 7.54 Hz, 2H), 3.05-3.14 (m, 2H), 3.18-3.24 (m, 1H), 3.59-3.65 (brm, 4H), 4.03-4.17 (m, 1H), 4.09 (t, J = 6.40 Hz, 2H), 4.73 (s, 1H), 5.80 (s, 1H), 7.51-7.65 (m, 3H), 7.76-7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 25.4, 27.0, 28.3 (2C), 39.9, 40.6, 42.3, 42.7, 50.4, 54.4, 59.0, 59.7, 63.3, 63.4, 80.6, 102.8, 127.2, 128.7, 129.2, 132.8, 137.3, 155.1, 155.9, 160.0, 171.0; IR (thin film) 3456, 2935, 2875, 1738, 1691, 1446, 1390, 1336, 1246, 1165, 1092, 1039, 978, 739, 692, 584 cm^{-1}; LRMS (FAB, M + Na): 611; HRMS Calculated for $C_{30}H_{40}N_2O_8S$ (FAB, M + Na): 611.2473. Found 611.2393; Anal. Calculated for $C_{30}H_{40}N_2O_8S$ C: 61.20, H: 6.85, N: 4.76, O: 21.74, S: 5.45. Found C: 61.08, H: 7.11, N: 4.57.

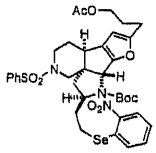




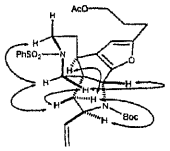
Optically pure (*S*)-**252** was prepared as same as racemic **252**. *tert*-Butyl (2*S*,3a*S*,7a*S*,10b*S*)-9-[3-(Acetyloxy)propyl]-2-(2-hydroxyethyl)-5-(phenylsulfonyl)-2,3,4,5 ,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carb oxylate [(*S*)-**252**]: $[\alpha]_D^{20}$ –29.0° (*c* 0.36, $CHCl_3$).

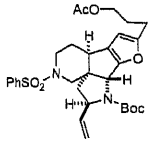
tert-Butyl (2*R**,3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-2-[2-(phenylseleno)ethyl]-5-(phenylsulf onyl)-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyr idine-1-carboxylate (**E-4**) and *tert*-Butyl (2*R**,3a*R**,7a*R**,10b*R**)-9-[3-(Acetyloxy)propyl]-5-(phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a ,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridine-1-carboxylat

e (253). To a solution of alcohol **252** (4.00 g, 6.79 mmol) and 2-nitrophenyl selenocyanate (1.85 g, 8.15 mmol) in THF (70 mL) was added tri-*n*-butylphosphine (1.37 g, 8.15 mmol) at 0 °C. After stirring for 16 h at rt, the reaction mixture was concentrated in vacuo and extracted with EtOAc (200 mL). Combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 70% EtOAc in *n*-hexane) to afford selenide **E-4** as a yellow syrup (5.44 g, 103%). A small amount of **E-4** was separated by preparative TLC. R_f= 0.36 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51-1.54 (m, 1H), 1.53(s, 9H), 1.90-2.00 (m, 5H), 2.05 (s, 3H), 2.14 (dd, J = 13.29, 8.32 Hz, 1H), 2.52 (brm, 1H), 2.64-2.69 (m, 1H), 2.66 (t, J = 7.35 Hz, 2H), 2.94 (brs, 2H), 3.16 (brs, 2H), 3.41 (brd, 1H), 3.90-3.98 (m, 1H), 4.09 (t, J = 6.41 Hz, 2H), 4.72 (s, 1H), 5.80 (s, 1H), 7.31 (brdt, J = 8.19, 1.14 Hz, 1H), 7.50-7.64 (m, 5H), 7.74-7.77 (m, 2H), 8.29 (dd, J = 8.24, 1.09 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 22.5, 25.4, 27.0, 27.5, 28.4, 33.8, 40.2, 41.4, 42.5, 50.4, 58.0, 58.6, 63.5 (2C), 80.2, 102.7, 125.3, 126.4, 127.2, 128.9, 129.2 (2C), 132.8, 133.6, 133.8, 137.3, 146.8, 154.6, 155.2, 160.2, 171.0; IR (thin film) 2972, 2931, 2871, 1736, 1689, 1589, 1566, 1512, 1477, 1446, 1389, 1365, 1333, 1304, 1248, 1159, 1138, 1095, 1038, 1095, 1038, 978, 912, 852, 785, 731, 690, 646, 582, 484, 432, 417 cm^{-1}; LRMS (FAB, M + Na): 774; HRMS Calculated for $C_{36}H_{43}N_3O_9SSe$ (FAB, M + Na): 796.1786. Found 796.1782.



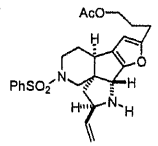
To a solution of selenide **E-4** (5.4 g) in CH_2Cl_2 (100 mL) and 2.4 M K_2HPO_4 (5 mL, 11.9 mmol) aqueous solution was added 70% *m*CPBA (1.67g, 6.77 mmol) portionwise at 0 °C. After stirring for 0.5 h at 0 °C, the reaction was quenched by addition of 1 *N* $Na_2S_2O_4$ (5 mL) aqueous solution and extracted with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ (20 mL, twice) aqueous solution and water (20 mL), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 65% EtOAc in *n*-hexane) to afford **253** as a yellow syrup (3.09 g, 80%): R_f= 0.52 (silica gel, EtOAc/*n*-hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.70 (m, 1H), 1.53 (s, 9H), 1.85-2.15 (m, 3H), 1.90-2.00 (m, 2H), 2.05 (s, 3H), 2.60-2.69 (m, 1H), 2.67 (t, J = 7.41 Hz, 2H), 2.95-3.25 (brm, 3H), 3.35-3.65 (brm, 1H), 4.09 (t, J = 6.42 Hz, 2H), 4.39 (brs, 1H), 4.71 (d, J = 0.82 Hz, 1H), 5.07-5.18 (m, 2H), 5.79 (s, 1H), 5.77-5.88 (m, 1H), 7.50-7.60 (m, 3H), 7.73-7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 25.5, 27.0, 27.9, 28.4, 39.8, 42.1, 42.2, 49.8, 59.2, 62.9, 63.5, 80.0, 102.8, 114.0, 127.3, 128.5, 129.1, 132.7, 137.6, 139.2, 154.3, 155.4, 160.3, 171.0; IR (thin film) 2960, 2929, 2856, 1738, 1695, 1387, 1346, 1244, 1169, 1092, 1038, 978, 741, 692, 582 cm^{-1}; LRMS (FAB, M + K): 609; HRMS Calculated for $C_{30}H_{38}N_2O_7S$ (FAB, M + K): 609.2037. Found 609.2051.

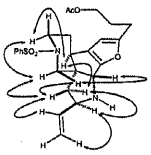




Optically pure (*S*)-253 was prepared as same as racemic 253. *tert*-Butyl (2*S*,3a*S*,7a*S*,10b*S*)-9-[3-(Acetyloxy)propyl]-5-(phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridine-1-carboxylate [(*S*)-253]: $[\alpha]_D^{20}$ –43.7° (*c* 0.43, $CHCl_3$).

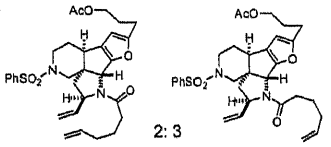
3-[(2*R**,3a*R**,7a*R**,10b*R**)-5-(Phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-9-yl]propyl Acetate (254) and 3-[(2*R**,3a*R**,7a*R**,10b*R**)-1-(5-Hexenoyl)-5-(phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-9-yl]propyl Acetate (255). To a solution of 253 (2.90 g, 5.08 mmol) in CH_2Cl_2 (8 mL) was added TFA (8 mL) at rt. After stirring for 0.5 h at rt, the mixture was concentrated in vacuo and extracted with EtOAc (50 mL), Combined organic layers were washed with sat. $NaHCO_3$ (15 mL, twice) aqueous solution and brine (15 mL), and concentrated in vacuo affording crude 254 as a reddish oil (2.70 g). A small amount of crude 254 was separated by preparative TLC (silica gel, EtOAc/*n*-hexane, 2:1). 3-[(2*R**,3a*R**,7a*R**,10b*R**)-5-(Phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-9-yl]propyl Acetate (254): R_f = 0.15 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.40 (m, 1H), 1.56-1.65 (m, 1H), 1.86-2.02 (m, 4H), 2.06 (s, 3H), 2.67 (t, J = 7.73 Hz, 2H), 2.71 (s, 1H), 2.79-2.83 (m, 1H), 3.12-3.22 (m, 2H), 3.14 (d, J = 12.35 Hz, 1H), 3.45 (d, J = 12.35 Hz, 1H), 3.50-3.58(m, 1H), 4.10 (t, J = 6.43 Hz, 2H), 4.30 (s, 1H), 5.05-5.19 (m, 2H), 5.78 (s, 1H), 5.80-5.90 (m, 1H), 7.48-7.59 (m, 3H), 7.75-7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 25.4, 26.2, 27.0, 41.1, 41.2, 47.4, 49.5, 60.1, 61.2, 63.6, 64.6, 102.5, 115.6, 127.1, 129.0, 129.1, 132.5, 138.1, 138.5, 155.2, 160.8, 171.1; IR (KBr) 3300, 3070, 2951, 2860, 1736, 1446, 1334, 1244, 1165, 1092, 1041, 970, 910, 733, 692, 588 cm^{-1}; LRMS (FAB, M + H): 471; HRMS Calculated for $C_{25}H_{31}N_2O_5S$ (FAB, M + H): 471.1954. Found 471.1967.





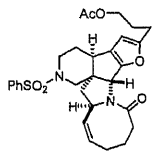
To a solution of 254 (1.76 g, 3.74 mmol), 5-hexenoic acid (470 mg, 4.11 mmol) and 1-hydroxybenzotriazole (HOBt) (286 mg, 1.87 mmol) in THF (9 mL) was added WSC·HCl (1.08 g, 5.61 mmol) at 0 °C for 1 h. After stirring for 3 h at rt, the reaction was quenched by addition of water (10 mL) and extracted with EtOAc (50 mL). Combined organic layers were washed with water (10 mL, twice) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 80% EtOAc in *n*-hexane) to afford amide 255 as a reddish oil (1.76 g, 83% from 253). 3-[(2*R**,3a*R**,7a*R**,10b*R**)-1-(5-Hexenoyl)-5-(phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-9-yl]propyl Acetate

(255): R_f= 0.56 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.65 (m, 5/5H), 1.7-2.35 (m, 47/5H), 2.04 (s, 6/5H), 2.06 (s, 9/5H), 2.45-2.81 (m, 21/5H), 2.84-2.93 (m, 21/5 H), 3.07-3.14 (m, 2/5H), 3.24-3.39 (m, 9/5H), 3.78 (brd, J = 12.76 Hz, 3/5H), 4.04-4.12 (m, 10/5H), 4.47-4.49 (m, 2/5H), 4.63-4.67 (m, 3/5H), 4.90-5.29 (m, 25/5H), 5.70-5.99 (m, 15/5H), 7.52-7.62 (m, 15/5H), 7.72-7.76 (m, 10/5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 24.1, 25.3, 26.8, 26.9, 27.7, 29.2, 33.1, 33.3, 33.4, 33.9, 39.1, 40.4, 41.1, 42.3, 42.4, 42.6, 49.0, 50.3, 58.0, 58.9, 59.9, 60.0, 62.5, 63.1, 63.3, 63.5, 102.5, 103.2, 113.9, 114.8, 114.9, 115.0, 127.1, 127.2, 128.2, 129.1, 129.4, 132.7, 132.7, 137.5, 137.5, 138.3, 138.9, 139.7, 154.1, 155.3, 160.5, 160.7, 171.0, 171.0, 172.8; IR (KBr) 2927, 2854, 1736, 1649, 1446, 1410, 1342, 1242, 1157, 1092, 1038, 978, 910, 742, 692, 582 cm^{-1}; LRMS (FAB, M + H): 567; HRMS Calculated for $C_{31}H_{39}N_2O_6S$ (FAB, M + H): 567.2529. Found 567.2602.



Optically pure (*S*)-**255** was prepared as same as racemic **255**. **3-[(2*S*,3a*S*,7a*S*,10b*S*)-1-(5-Hexenoyl)-5-(phenylsulfonyl)-2-vinyl-2,3,4,5,6,7,7a,10b-octahydro-1*H*-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-*c*]pyridin-9-yl]propyl Acetate** [(*S*)-**255**]: $[\alpha]_D^{20}$ –38.7° (*c* 0.46, $CHCl_3$).

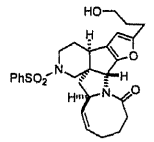
3-[(6a*R,7a*R**,11a*R**,14b*R**)-1-Oxo-9-(phenylsulfonyl)-1,2,3,4,6a,7,8,9,10,11,11a,14b-dodecahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-13-yl]propyl Acetate (263).** A solution of **255** (200 mg, 0.35 mmol) in degassed (three freeze-thaw cycles) CH_2Cl_2 (350 mL) containing catalyst **213** (45.0 mg, 53.0 μmol) was heated under reflux for 2 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (silica gel, 10% to 100% EtOAc in *n*-hexane) to afford **263** as a colorless foam (147 mg, 86%): R_f= 0.18 (silica gel, EtOAc/*n*-hexane, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40-1.53 (m, 1H), 1.60-1.82 (m, 1H), 1.83-2.08 (m, 6H), 2.04 (s, 3 H), 2.17-2.39 (m, 2H), 2.36 (dd, J = 13.63, 4.19 Hz, 1H), 2.54-2.61 (m, 1H), 2.63-2.72 (m, 1H), 2.69 (t, J = 7.46 Hz, 2H), 2.95-3.04 (m, 1H), 3.01 (d, J = 12.59 Hz, 1H), 3.26-3.33 (m, 1H), 3.51 (d, J = 12.59 Hz, 1H), 4.07 (t, J = 6.43 Hz, 2H), 4.58 (brd, J = 9.36 Hz, 1H), 5.07(s, 1H), 5.46 (br dt, J = 11.95, 2.01 Hz, 1H), 5.76 (ddd, J = 11.95, 9.36, 1.99 Hz, 1H), 5.81 (s, 1H), 7.49-7.62 (m, 3H), 7.72-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 22.8, 25.4, 26.3, 26.9, 29.1, 32.6, 39.0, 43.0, 43.1, 49.6, 56.8, 59.7, 63.0, 63.6, 102.7, 127.3 (2C), 129.1, 129.2, 132.7, 133.9, 137.5, 155.2, 160.5, 171.1, 173.3; IR (thin film) 2931, 2858, 1734, 1645, 1464, 1408, 1340, 1242, 1161, 1092, 1043, 982, 775, 742, 692, 580 cm^{-1}; LRMS (FAB, M + H): 359; HRMS Calculated for $C_{29}H_{35}N_2O_6S$ (FAB, M + H): 539.2216. Found 539.2187; Anal. Calculated



for $C_{29}H_{34}N_2O_6S.H_2O$, C: 62.57, H: 6.52, N: 5.03, O: 20.12, S: 5.76. Found C: 63.32, H: 6.43, N: 5.06.

Optically pure (*S*)-**263** was prepared as same as racemic **263**. **3-[(6a*S*,7a*S*,11a*S*,14b*S*)-1-Oxo-9-(phenylsulfonyl)-1,2,3,4,6a,7,8,9,10,11,11a,14b-dodecahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-13-yl]propyl Acetate [(*S*)-263]**: $[\alpha]_D^{20}$ –90.7° (*c* 0.46, $CHCl_3$). Optical purity of **263** was confirmed by HPLC analysis using a chiral column. A racemic form of **263** was subjected to HPLC analysis (column: Chiralpak AD column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent *n*-hexane/EtOH, 75:25; flow rate, 1.0 mL/min; temperature, 40 °C; detector, 254 nm) and peaks due to (*S*)-(-)-and (*R*)-(+)-**263** were detected at t_R 11.4 and 22.9 min.

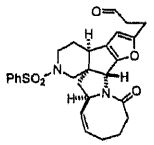
(6a*R,7a*R**,11a*R**,14b*R**)-13-(3-Hydroxypropyl)-9-(phenylsulfonyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one (265)**. To a solution of ester **263** (294 mg, 0.59 mmol) in MeOH (10 mL) was added 2 *N*NaOH (4.0 mL, 8.00 mmol) aqueous solution at rt. After stirring for 1.0 h at rt, the reaction mixture was concentrated in vacuo and extracted with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 100% EtOAc in *n*-hexane) to afford alcohol **265** as a colorless solid (248 mg, 92%): R_f = 0.17 (silica gel, EtOAc); mp 200-203 °C dec.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.58 (m, 1H), 1.70-1.77 (m, 2H), 1.77-1.93 (m, 2H), 1.98-2.08 (m, 4H), 2.13-2.38 (m, 3H), 2.49-2.71 (m, 2H), 2.71 (t, J = 7.36 Hz, 2H), 2.94-3.14 (m, 1H), 3.04 (d, J = 12.57 Hz, 1H), 3.24-3.31 (m, 1H), 3.49 (d, J = 12.57 Hz, 1H), 3.68 (t, J = 6.17 Hz, 2H), 4.58 (brd, J = 9.17 Hz, 1H), 5.05 (s, 1H), 5.47 (brdt, J = 12.09 Hz, 1H), 5.71-5.85 (m, 2H), 5.81 (s, 1H), 7.50-7.62 m, 3H), 7.73-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.3, 26.3, 28.9, 31.0, 32.6, 39.1, 43.0, 43.1, 49.6, 56.8, 59.8, 62.1, 63.1, 102.5, 127.3, 127.4, 129.1, 129.2, 132.7, 133.8, 137.5, 155.1, 161.3, 173.4; IR (thin film) 3400, 2941, 2873, 1628, 1464, 1446, 1415, 1340, 1159, 982, 910, 777, 735, 692, 580 cm^{-1}; LRMS (FAB, M + H): 497; HRMS Calculated for $C_{27}H_{33}N_2O_5S$ (FAB, M + H): 497.2110. Found 497.2101; Anal. Calculated for $C_{27}H_{32}N_2O_5S$ 1/4 H_2O, C: 64.71, H: 6.54, N: 5.59, O: 16.76, S: 6.40. Found C: 64.75, H: 6.56, N: 5.55.



Optically pure (*S*)-**265** was prepared as same as racemic **265**. **(6a*S*,7a*S*,11a*S*,14b*S*)-13-(3-Hydroxypropyl)-9-(phenylsulfonyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one [(*S*)-265]**: mp 177.5-178.5 °C (EtOAc/diisopropyl ether); $[\alpha]_D^{20}$ –104.3° (*c* 0.56, $CHCl_3$). Optical purity of **265** was confirmed by HPLC analysis using a chiral column. A

racemic form of **265** was subjected to HPLC analysis (column: Chiralpak AD column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent *n*-hexane/EtOH, 75:25; flow rate, 1.0 mL/min; temperature, 40 °C; detector, 254 nm) and peaks due to (*S*)-(-)-and (*R*)-(+)-**265** were detected at t_R 8.8 and 20.7 min.

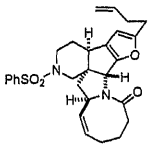
3-[(6a*R,7a*R**,11a*R**,14b*R**)-1-Oxo-9-(phenylsulfonyl)-1,2,3,4,6a,7,8,9,10,11,11a,14b-dodecahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-13-yl]propanal (266).** To a solution of alcohol **265** (898 mg, 1.81 mmol) in CH_2Cl_2 (70 mL) was added Dess-Martin periodinane (805 mg, 1.90 mmol) at 3 °C. After stirring for 1.5 h at 3 °C, the reaction was quenched by addition of 1 *N* $Na_2S_2O_3$ (4 mL) aqueous solution and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 28% to 100% EtOAc in *n*-hexane) to afford aldehyde **266** as a colorless solid (718 mg, 80%): R_f = 0.37 (silica gel, EtOAc); mp 197.5-198.5 °C (EtOAc/*n* pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39-1.53 (m, 1H), 1.69-1.78 (m, 1H), 1.97-2.09 (m, 4H), 2.22-2.29 (brm, 1H), 2.29-2.39 (m, 1H), 2.31 (dd, J = 12.95, 7.59 Hz, 1H), 2.54-2.59 (m, 1H), 2.61-2.69 (m, 1H), 2.80 (dt, J = 7.03, 0.96 Hz, 2H), 2.93-3.03 (m, 1H), 2.95 (t, J = 7.03 Hz, 2H), 2.97 (d, J = 12.57 Hz, 1H), 3.12-3.33 (m, 1H), 3.52 (d, J = 12.57 Hz, 1H), 4.57 (brd, J = 9.44 Hz, 1H), 5.07 (s, 1H), 5.46 (brdt, J = 12.05, 2.21, 2.21 Hz, 1H), 5.76 (ddd, J = 12.05, 9.32, 2.23 Hz, 1H), 5.82 (s, 1H), 7.49-7.62 (m, 3H), 7.72-7.76 (m, 2H), 9.79 (d, J = 0.96 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.8, 26.3, 29.0, 32.5, 39.0, 41.8, 43.0, 43.1, 49.6, 56.8, 59.7, 63.0, 103.2, 127.3, 127.4, 129.1, 129.3, 132.7, 133.8, 137.5, 155.5, 159.3, 173.4, 201.0; IR (thin film) 3012, 2941, 2860, 1722, 1637, 1464, 1412, 1340, 1161, 1092, 982, 910, 777, 737, 692, 580 cm^{-1}; LRMS (FAB, M + H): 495; HRMS Calculated for $C_{27}H_{31}N_2O_5S$ (FAB, M + H): 495.1954. Found 495.1954; Anal Calculated for $C_{27}H_{30}N_2O_5S$. H_2O, C: 63.26, H: 6.29, N: 5.46, O: 18.73, S: 6.26. Found C: 63.67, H: 5.97, N: 5.09.

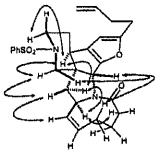


Optically pure (*S*)-**266** was prepared as same as racemic **266**. **3-[(6a*S*,7a*S*,11a*S*,14b*S*)-1-Oxo-9-(phenylsulfonyl)-1,2,3,4,6a,7,8,9,10,11,11a,14b-dodecahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-13-yl]propanal [(*S*)-266]:** $[\alpha]_D^{20}$ −193.4° (*c* 0.58, $CHCl_3$).

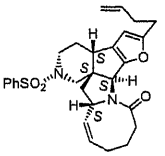
(6a*R,7a*R**,11a*R**,14b*R**)-13-(3-Butenyl)-9-(phenylsulfonyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one (267).** A 0.5 M solution of potassium bis(trimethylsilyl)amide (7.2 mL, 3.61 mmol) in toluene was added dropwise to a solution of methyltriphenylphosphonium

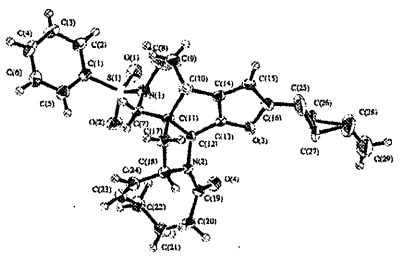
bromide (992 mg, 2.78 mmol) in toluene (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 0.5 h to give a solution of the Wittig reagent. The solution of Wittig reagent (12 mL) was added dropwise to a solution of aldehyde **266** (687 mg, 1.39 mmol) in THF (20 mL) at 0 °C for 2 h. After stirring for 1.5 h at rt, the reaction was quenched by addition of sat. NH_4Cl aqueous solution and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), and the solution was washed with water (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% to 90% EtOAc in *n*-hexane) to afford **267** as a colorless solid (492 mg, 72%): R_f = 0.45 (silica gel, EtOAc); mp 172-175 °C dec. (EtOAc/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.54 (m, 1H), 1.68-1.79 (m, 1H), 1.95-2.08 (m, 4H), 2.23-2.41 (m, 5H), 2.54-2.73 (m, 4H), 2.92-3.01 (m, 1H), 2.96 (d, J = 12.57 Hz, 1H), 3.27-3.34 (m, 1H), 3.54 (d, J = 12.57 Hz, 1H), 4.57 (brd, J = 9.37 Hz, 1H), 4.95-5.10 (m, 2H), 5.09 (s, 1H), 5.45 (ddd, J = 12.05, 2.05, 2.05 Hz, 1H), 5.73-5.83 (m, 2H), 5.80 (s, 1H), 7.49-7.59 (m, 3H), 7.72-7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 26.3, 28.3, 29.1, 31.8, 32.5, 38.9, 43.0, 43.1, 49.6, 56.6, 59.6, 62.9, 102.3, 115.1, 127.2, 127.3, 129.1, 129.1, 132.7, 133.8, 137.4, 137.4, 154.9, 161.2, 173.2; IR (thin film) 3070, 3010, 2939, 2873, 2858, 1641, 1462, 1408, 1342, 1159, 1092, 982, 910, 775, 735, 690, 579 cm^{-1}; LRMS (FAB, M + H) 493; HRMS Calculated for $C_{28}H_{33}N_2O_4S$ (FAB, M + H): 493.2161. Found 493.2140; Anal. Calculated for $C_{28}H_{32}N_2O_4S$ C: 68.27, H: 6.55, N: 5.69, O: 12.99, S: 6.51. Found C: 68.39, H: 6.63, N: 5.63.





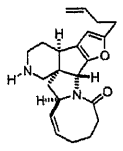
Optically pure (*S*)-**267** was prepared as same as racemic **267**. **(6a*S*,7a*S*,11a*S*,14b*S*)-13-(3-Butenyl)-9-(phenylsulfonyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one [(*S*)-267]**: mp 214.0-215.0 °C (EtOH); $[\alpha]_D^{20}$ −93.1° (*c* 0.66, $CHCl_3$). Optical purity of **267** was confirmed by HPLC analysis using a chiral column. A racemic form of **267** was subjected to HPLC analysis (column: Chiralpak AD column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent *n*-hexane/EtOH, 75:25; flow rate, 1.0 mL/min; temperature, 40 °C; detector, 254 nm) and peaks due to (*S*)-(-)-and (*R*)-(+)-**267** were detected at t_R 7.8 and 17.5 min. Crystal data: $C_{28}H_{32}N_2O_4S$, FW=492.63, orthorhombic system, a = 10.780 (2) Å, b = 12.270 (2) Å, c = 18.705 (4) Å, V = 2474.2 (7) Å^3, space group $P2_12_12_1$ (#19), Z value = 4, D_{calc} = 1.322 g/cm^3, F_{000} = 1048.00, μ (MoKα) 1.69 cm^{-1}, Lattice constants and intensity data were measured using graphite monochromated MoKα (λ = 0.71069 Å) radiation on





graphite monochromated diffractometer. Of the 14949 reflections which were collected, 3399 were unique (R_{int} = 0.087). These were made on a Rigaku/MSC Mercury diffractometer. The structure was solved by direct methods using SIR92 and refined to a final R value of 0.062 and Rw = 0.082.

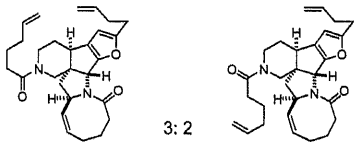
(6a*R*,7a*R***,11a*R***,14b*R***)-13-(3-Butenyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one (269) and (6a*R***,7a*R***,11a*R***,14b*R***)-13-(3-Butenyl)-9-(5-hexenoyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one** (270). A 0.39 M solution of sodium naphthalenide in DME was prepared by stirring a mixture of sodium metal (409 mg, 17.79 mmol) and naphthalene (2.28g, 17.79 mmol) in dry DME (40 mL) at rt for 4 h. The solution maintained a deep blue color. This naphthalenide solution (0.9 mL) was added dropwise to a solution of **267** (57 mg, 0.116 mmol) in DME (8 mL) at –78 °C until a blue color persisted for 30 min. The reaction was quenched by addition of sat. NH_4Cl (2 mL) aqueous solution and the mixture was concentrated in vacuo. The residue was dissolved in 1 *N* HCl (20 mL) aqueous solution and the solution was washed with EtOAc (5 mL, twice) repeatedly. The aqueous layer was basified to pH 8 with 2 *N* NaOH (20 mL) aqueous solution and extracted with EtOAc (30 mL, twice). Combined organic layers were washed with 1 *N* NaOH (10 mL) aqueous solution and brine (20 mL), concentrated in vacuo to afford crude amine **269** (36 mg, 88%). **(6a*R***,7a*R***,11a*R***,14b*R***)-13-(3-Butenyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one** (269): R_f = 0.06 (silica gel, EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.28 (m, 1H), 1.64-1.76 (m, 1H), 1.78 (dd, J= 13.85, 2.11 Hz, 1H), 1.94-2.21 (m, 4H), 2.26-2.47 (m, 5H), 2.53-2.73 (m, 6H), 2.86-2.95 (m, 1H), 3.25 (d, J = 13.60 Hz, 1H), 4.50-4.54 (m, 1H), 4.95-5.08 (m, 2H), 5.20 (s, 1H), 5.40 (dt, J = 12.09, 2.21, 2.17 Hz, 1H), 5.58-5.69 (m, 1H), 5.77-5.91 (m, 1H), 5.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 26.1, 28.3, 29.6, 31.9, 32.6, 32.7, 38.8, 43.6, 44.4, 52.8, 54.9, 59.7, 62.5, 102.5, 115.0, 126.2, 131.4, 134.4, 137.6, 155.1, 160.4, 173.4; IR (thin film) 3450, 3350, 2933, 2858, 1639, 1464, 1415, 1188, 1159, 916, 798, 729 cm^{-1}; LRMS (FAB, M + H): 353; HRMS Calculated for $C_{22}H_{29}N_2O_2$ (FAB, M + H): 353.2229. Found 353.2225.



Optically pure (*S*)-**269** was prepared as same as racemic **269**. **(6a*S*,7a*S*,11a*S*,14b*S*)-13-(3-Butenyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one** [(*S*)-**269**]: $[\alpha]_D^{20}$ –162.8° (*c* 0.43, $CHCl_3$). To a solution of 5-hexenoic acid (12 mg, 0.143 mmol), HOBt

(7.2 mg, 46.8 μmol) and amine **269** (33 mg, 93.6 μmol) in THF (1.5 mL) was added WSC•HCl (27 mg, 0.14 mmol) at 3 °C for 0.5 h. After stirring for 2.5 h at rt, the reaction was quenched by addition of water (3 mL) and extracted with EtOAc. Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc) to afford amide **270** as a colorless oil (37 mg, 88%).

(6a*R*,7a*R***,11a*R***,14b*R***)-13-(3-Butenyl)-9-(5-hexenoyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one (270)**: R_f = 0.36 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-1.90 (m, 25/5H), 1.94-2.45 (m, 60/5H), 2.59-2.75 (m, 20/5H), 3.19-3.55 (m, 10/5H), 3.36 (d, J = 13.77 Hz, 3/5H), 3.46 (d, J = 13.61 Hz, 2/5H), 3.68 (d, J = 13.61 Hz, 2/5H), 4.17 (d, J = 13.77 Hz, 3/5H), 4.58-4.66 (m, 5/5H), 4.90-5.09 (m, 25/5H), 5.46-5.53 (m, 5/5H), 5.70-5.91 (m, 20/5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.1, 23.9, 24.1, 26.5, 26.7, 26.9, 27.3, 28.4, 31.9, 32.5, 32.6, 32.7, 32.9, 33.3, 33.4, 39.8, 40.1, 40.6, 41.1, 43.1, 43.5, 43.9, 48.0, 57.4, 57.6, 59.7, 63.6, 63.6, 102.4, 102.5, 115.1, 115.1, 127.5, 127.9, 128.0, 128.6, 133.4, 134.3, 137.5, 137.5, 138.1, 138.2, 154.6, 155.3, 161.8, 161.9, 172.1, 172.8, 173.3, 173.6,; IR (thin film) 2929, 2858, 1641, 1460, 1417, 1271, 1194, 1157, 993, 912 cm^{-1}; LRMS (FAB, M + H): 449; HRMS Calculated for $C_{28}H_{37}N_2O_3$ (FAB, M + H): 449.2804. Found 449.2812.

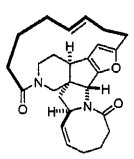


Optically pure (*S*)-**270** was prepared as same as racemic **270**.

(6a*S*,7a*S*,11a*S*,14b*S*)-13-(3-Butenyl)-9-(5-hexenoyl)-3,4,6a,7,8,9,10,11,11a,14b-decahydrofuro[2",3":3',4']pyrido[3",4":1',5']cyclopenta[1',2':4,5]pyrrolo[1,2-*a*]azocin-1(2*H*)-one [(*S*)-270]: $[\alpha]_D^{20}$ −78.3° (*c* 0.46, $CHCl_3$).

20,29-Dioxonakadomarin A (271). A solution of **270** (192 mg, 0.43 mmol) in degassed (three freeze-thaw cycles) CH_2Cl_2 (700 mL) containing catalyst **214** (52.8 mg, 64.2 μmol) was heated under reflux for 24 h. The mixture was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc) to give (24*E*)-**271** (78.4 mg, 44%) and (24*Z*)-**271** (43.1 mg, 24%) as a colorless solid. The structure of (24*E*)-**271** was established by nOe study (see Supporting Information).

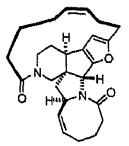
Less Polar (24*E*)-271: R_f = 0.26 (silica gel, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.57 (m, 2H), 1.61-2.11 (m, 9H), 2.15-1.99 (m, 4H) 2.32-2.49 (m, 1H), 2.54-2.74 (m, 3H), 2.83-3.93 (m, 1H), 2.86 (d, J = 13.71 Hz, 1H), 3.04 (brs, 1H), 3.20-3.29 (m, 1H), 3.30-3.39 (m, 1H), 4.43-4.50 (m, 1H), 4.60 (d, J = 13.71 Hz, 1H), 4.99 (s, 1H), 5.16-5.30 (m, 2H), 5.48-5.64 (m, 2H), 5.81 (s, 1



H); ^{1}H NMR (300 MHz, MeOH-d_4) δ 1.41-1.54 (m, 2 H), 1.59-1.86 (m, 4 H), 1.64 (dd, J = 12.95, 11.51 Hz, 1H), 1.90-2.19 (m, 6H), 2.20-2.40 (m, 2H), 2.33 (dd, J = 12.95, 5.53 Hz, 1H), 2.47-2.60 (m, 1H), 2.62-2.80 (m, 3H), 3.01 (d, J = 13.67 Hz, 1H), 3.12 (s, 1H), 3.26-3.43 (m, 2H), 4.44 (d, J = 13.67 Hz, 1H), 4.55 (m, 1H), 5.12 (s, 1H), 5.11-5.20 (m, 1H), 5.23-5.37 (m, 1H), 5.58 (ddd, J = 11.96, 11.14, 8.29 Hz, 1H), 5.69 (ddd, J = 11.96, 4.02, 1.19 Hz, 1H), 5.96 (s, 1H); ^{1}H NMR (300 MHz, C_6D_6) δ 1.05-1.25 (m, 1H), 1.33 (dd, J = 13.53, 11.23 Hz, 1H), 1.51-1.80 (m, 8H), 1.84-1.97 (m, 1H), 2.08-2.15 (m, 1H), 2.22-2.54 (m, 6H), 2.48 (d, J = 13.61 Hz, 1H), 2.58-2.79 (m, 3H), 2.69 (brs, 1H), 3.00-3.10 (m, 1H), 4.03-4.08 (m, 1H), 4.82 (d, J = 13.61 Hz, 1H), 5.20-5.32 (m, 4H), 5.53 (s, 1H), 5.63 (s, 1H, furan H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.8, 22.7, 23.7, 28.3, 29.5, 31.1, 31.1, 32.4, 39.6, 40.4, 43.3, 44.8, 58.2, 58.7, 65.8, 102.6, 125.8, 129.0, 130.3, 131.1, 131.5, 157.2, 160.7, 172.1, 172.5; ^{13}C NMR (75 MHz, MeOH-d_4) δ 22.2, 22.2, 23.4, 24.5, 29.1, 30.4, 32.0, 32.3, 33.1, 40.6, 42.0, 44.0, 46.1, 59.6, 60.4, 67.3, 104.3, 126.3, 131.5, 131.8, 132.2, 132.4, 157.5, 162.0, 174.7, 175.0; IR (thin film) 3014, 2939, 2877, 1639, 1456, 1429, 1350, 1265, 1159, 1074, 1001, 968, 910, 845, 787, 727 cm^{-1}; LRMS (FAB, M + H): 420; HRMS Calculated for $C_{26}H_{33}N_2O_3$ (FAB, M + H): 421.2491. Found 420.2471.

Optically pure (*S*)-(24*E*)-**271** was prepared as same as racemic (24*E*)-**271**. **(*S*)-(-)-24*E*-20,29-Dioxonakadomarin A** [(*S*)-(24*E*)-**271**]: $[\alpha]_D^{20}$ −56.8° (*c* 0.62, $CHCl_3$). Optical purity of **271** was confirmed by HPLC analysis using a chiral column. A racemic form of **271** was subjected to HPLC analysis (column: Chiralpak AD column, 4.6 i. d. X 250 mm, Daicel Chemical Ind., Ltd.; eluent *n*-hexane/EtOH, 75:25; flow rate, 1.0 mL/min; temperature, 40 °C; detector, 206 nm) and peaks due to (*S*)-(-)-and (*R*)-(+)-**271** were detected at t_R 6.7 and 7.2 min.

More Polar (24*Z*)-271: R_f = 0.14 (silica gel, EtOAc); mp 161-162 °C dec.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.93 (m, 9H), 2.00-2.45 (m, 8H), 2.58-2.68 (m, 2H), 2.88 (d, J = 13.71 Hz, 1H), 2.86-2.95 (m, 1H), 3.05 (brs, 1H), 3.15-3.25 (m, 1H), 3.29-3.35 (m, 1H), 4.42-4.49 (m, 1H), 4.52 (d, J = 13.71 Hz, 1H), 5.01 (s, 1H), 5.21-5.32 (m, 2H), 5.54 (dd, J = 11.84, 8.03 Hz, 1H), 5.63 (dd, J = 11.84, 3.98 Hz, 1H), 5.73 (s, 1H); ^{1}H NMR (300 MHz, MeOH-d_4) δ 1.38-1.92 (m, 8H), 1.95-2.25 (m, 5H), 2.26-2.45 (m, 3H), 2.48-2.63 (m, 2H), 2.70-2.80 (m, 2H), 3.03 (d, J = 13.71 Hz ,1H), 3.13 (brs, 1H), 3.21-3.31 (m, 1H), 3.37-3.43 (m, 1H), 4.47 (d, J = 13.71 Hz, 1H), 4.51-4.57 (m, 1H), 4.95 (s, 1H), 5.26-5.35 (m, 2H), 5.59 (ddd, J = 11.84, 8.10, 8.10 Hz, 1H), 5.73 (ddd, J = 11.84, 4.33, 1.22 Hz, 1H), 5.87 (s, 1H); ^{1}H NMR (300 MHz, C_6D_6) δ 1.12-1.28 (m,1H), 1.33-1.62 (m, 6H), 1.64-1.96 (m, 6H), 2.07-2.34 (m, 4H), 2.38-2.50 (m, 1H), 2.49 (d, J = 13.58 Hz, 1H), 2.56-2.77 (m, 1H), 2.67 (brs, 1H), 2.78-2.82 (m, 2H), 2.95-3.06 (m, 1H), 4.02-4.08 (m, 1H), 4.85 (d, J = 13.58 Hz, 1H), 5.19-5.35 (m, 4H), 5.61 (s, 1H), 5.65 (s, 1H);

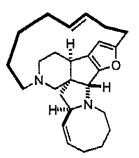


^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 22.6, 23.9, 24.00, 25.6, 27.4, 28.3, 29.9, 32.6, 39.9, 40.9, 44.3, 44.6, 57.3, 58.5, 65.8, 103.4, 126.3, 129.3, 129.5, 130.9, 131.5, 156.7, 160.8, 172.2, 173.3; ^{13}C NMR (75 MHz, MeOH-d_4) δ 22.9, 23.4, 24.6, 25.2, 26.5, 28.4, 29.1, 30.9, 33.2, 40.9, 42.5, 44.9, 45.9, 58.6, 60.3, 67.2, 105.0, 126.7, 130.6, 131.8, 132.3 (2C), 157.1, 162.1, 174.8, 175.7; ^{13}C NMR (75 MHz, C_6D_6) δ 21.1, 21.8, 22.7, 24.0, 28.6, 29.8, 31.3, 31.8, 32.6, 39.5, 39.8, 43.4, 44.9, 58.2, 58.4, 66.0, 102.7, 125.8, 128.9, 130.4, 131.2, 131.90, 158.3, 160.6, 171.0, 171.8; IR (thin film) 3003, 2920, 2860, 1730, 1556, 1456, 1419, 1350, 1267, 1211, 1159, 1068, 1028, 953, 910, 849, 787, 725 cm^{-1}; LRMS (FAB, M + H): 420; HRMS Calculated for $C_{26}H_{33}N_2O_3$ (FAB, M + H): 421.2491. Found 420.2497.

Optically pure (*S*)-**271** was prepared as same as racemic **271**.

(*S*)-(-)-20,29-Dioxonakadomarin A: $[\alpha]_D^{20}$ –75.7° (*c* 0.37, $CHCl_3$).

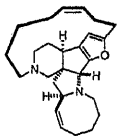
24*E*-Nakadomarin A [(24*E*)-**1**]. A 70% solution of Red-Al in toluene (0.5 mL) was added dropwise to a solution of 20, 29-dioxonakadomarin A (48 mg, 1.14 mmol) in toluene (20 mL) under 5 °C and stirring was continued for 10 min. After the solution was heated under reflux for 2.5 h, the solution was cooled to –30 °C. To this mixture was added sat. Rochelle's salt (20 mL), and the mixture was stirred vigorously for 1 h at rt. Then the mixture was diluted with H_2O (5 mL), and extracted with EtOAc (10 mL). Combined extracts were concentrated in vacuo to give a residue which was purified by column chromatography (silica gel, 66% MeOH in EtOAc) to give (24*E*)-**1** as a colorless film (30 mg, 63%): R_f = 0.24 (silica gel, EtOAc/MeOH, 1:3); ^{1}H NMR (600 MHz, MeOH-d_4) δ 1.03-1.10 (m, 1H), 1.12-1.18 (m, 1H), 1.20-1.33 (m, 3H), 1.36-1.44 (m, 1H), 1.47-1.52 (m, 1H), 1.56-1.73 (m, 4H), 1.79-1.84 (m, 1H), 1.89-1.92 (m, 1H), 1.96-2.02 (m, 1H), 2.02-2.10 (m, 3H), 2.17-2.20 (m, 1H), 2.23-2.34 (m, 2H), 2.31 (d, J = 12.10 Hz, 1H), 2.38-2.45 (m, 2H), 2.61-2.71 (m, 2H), 2.75-2.80 (m, 2H), 2.85 (brs, 1H), 3.02-3.53 (m, 1H), 3.07 (d, J = 12.10 Hz, 1H), 3.67~3.74 (m, 1H), 4.04 (s, 1H), 5.21-5.27 (m, 2H), 5.47-5.50 (m, 1H), 5.79-5.84 (m, 1H), 5.91 (s, 1H); ^{1}H NMR (600 MHz, C_6D_6) δ 0.99-1.06 (m, 1H), 1.12-1.44 (m, 5H), 1.44-1.53 (m, 1H), 1.56-1.60 (m, 1H), 1.63-1.82 (m, 5H), 1.93-2.03 (m, 2H), 2.03-2.22 (m, 3H), 2.17 (d, J = 11.82 Hz, 1H), 2.28-2.33 (m, 2H), 2.48-2.68 (m, 4H), 2.63 (brs, 1H), 2.84 (d, J = 11.82 Hz, 1H), 2.89-2.98 (m, 1H), 3.19-3.24 (m, 1H), 3.57-3.61 (m, 1H), 4.34 (s, 1H), 5.30 (ddd, J = 14.85, 7.70, 1.92 Hz, 1H), 5.35 (ddd, J = 14.85, 8.35, 5.77 Hz, 1H), 5.56 (ddd, J = 7.97, 16.12, 2.47 Hz, 1H), 5.61 (ddd, J = 7.97, 10.59, 0.00 Hz, 1H), 5.72 (s, 1H); ^{13}C NMR (150 MHz, MeOH-d_4) δ 24.5, 24.7, 26.4, 27.6, 27.87, 27.9, 29.4, 32.0, 33.3, 41.8, 42.7, 45.1, 49.5, 56.6, 58.1, 58.9, 61.7, 73.2, 102.8, 127.9, 130.0, 132.3, 133.5, 133.6, 153.9, 161.5; ^{13}C NMR (150 MHz, C_6D_6) δ 22.3, 25.2, 26.6, 27.0, 27.6, 28.0, 28.6, 29.9, 32.4, 33.9, 41.4, 44.2, 45.6, 50.8, 58.3,



59.1, 59.5, 61.9, 73.7, 102.8, 127.8 (peak of benzene was overlapped), 129.3, 132.4, 132.7, 147.9, 160.6; IR (thin film) 2921, 2854, 2790, 1442, 1132, 958; LRMS (FAB, M + H): 393; HRMS Calculated for $C_{26}H_{37}N_2O$ (FAB, M + H): 393.2906. Found 393.2891.

Optically pure (*S*)-(24*E*)-**1** was prepared as same as racemic (24*E*)-**1**. **(*S*)-(+)-24*E*-Nakadomarin A (free) (synthetic)** [(*S*)-(24*E*)-**1**]: $[\alpha]_D^{25}$ +75.2° (*c* 1.00, MeOH).

Nakadomarin A (**1**): A 70% solution of Red-Al in toluene (0.2 mL) was added dropwise to a solution of 20, 29-dioxonakadomarin A (20 mg, 47.5 μmol) in toluene (8 mL) under 5 °C and stirring was continued for 10 min. After the solution was heated under reflux for 2.5 h, the solution was cooled to – 30 °C. To this mixture was added sat. Rochelle's salt (7 mL), and the mixture was stirred vigorously for 1 h at rt. Then the mixture was diluted with H_2O (5 mL), and extracted with EtOAc (20 mL). Combined extracts were concentrated in vacuo to give a residue which was purified by column chromatography (silica gel, 66% MeOH in EtOAc) to afford **1** as a colorless film (16 mg, 86%): R_f = 0.22 (silica gel, EtOAc/MeOH, 1:3); ^{1}H NMR (300 MHz, MeOH-d_4) δ 0.80-0.99 (m, 1H), 1.01-1.29 (m, 2H), 1.28-1.45 (m, 2H), 1.49 (dd, J = 10.38, 12.16 Hz, 1H), 1.55-1.73 (m, 4H), 1.76-2.20 (m, 7H), 2.26-2.54 (m, 3H), 2.31 (d, *J* = 12.06 Hz, 1H), 2.57-2.79 (m, 5H), 2.84 (brs, 1H), 2.98-3.06 (brm, 1H), 3.05 (d, *J* = 12.06 Hz, 1H), 3.63-3.89 (brm, 1H), 3.94 (brs, 1H), 2.27 (brdd, J = 18.68, 10.66 Hz, 1H), 5.40-5.53 (m, 2H), 5.81 (brdd, J = 17.90, 8.63 Hz, 1H), 5.87 (s, 1H); ^{1}H NMR (600 MHz, MeOH-d_4) δ 0.84-0.93 (m, 1H), 1.02-1.11 (m, 2H), 1.27-1.36 (m, 1H), 1.36-1.44 (m, 1H), 1.49 (dd, J = 12.37, 10.17 Hz, 1H, H-13β), 1.57-1.75 (m, 4H), 1.81-1.84 (m, 1H), 1.88-1.96 (m, 2H), 1.97-2.05 (m, 1H), 2.05-2.11 (m, 1H), 2.12-2.18 (m, 2H), 2.29-2.36 (m, 3H), 2.38-2.43 (m, 1H), 2.45-2.53 (m, 1H), 2.59-2.65 (m, 2H), 2.69-2.75 (m, 1H), 2.75-2.82 (m, 1H), 2.84 (brs, 1H), 2.99-3.07 (m, 1H), 3.05 (d, J = 12.10 Hz, 1H), 3.71-3.77 (m, 1H), 3.94 (s, 1H), 5.26 (ddd, J = 10.9, 8.8, 8.2 Hz, 1H), 5.44 (dt, J = 10.9, 8.0 Hz, 1H), 5.50 (brt, J = 9.4, 8.5 Hz, 1H), 5.81 (brq, J = 9.4, 17.1 Hz, 1H), 5.87 (s, 1H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 23.0, 25.9, 26.0, 27.1, 27.2, 28.3, 29.2, 29.2, 29.5, 43.1, 43.4, 46.1, 50.9, 58.3, 59.3, 60.6, 63.6, 74.7, 104.7, 129.3, 131.5, 132.3, 134.6, 135.3, 156.5, 162.5; IR (thin film) 2922, 2856, 2787, 2740, 1442, 1134 cm^{-1}; ^{13}C NMR (150 MHz, MeOH-d_4) δ 21.6, 24.55, 24.64, 25.78, 25.84, 27.5, 27.9, 28.2, 29.4, 41.8, 42.1, 44.7, 49.6, 57.0, 57.9, 59.3, 62.3, 73.4, 103.4, 127.9, 130.1, 130.9, 133.3, 133.9, 155.1, 161.1; LRMS (FAB, M + H): 393; HRMS Calculated for $C_{26}H_{37}N_2O$ (FAB, M + H): 393.2906. Found 393.2914.



Optically pure *Ent*-(*S*)-**1** was prepared as same as racemic **1**. ***Ent*-(*S*)-(+)-Nakadomarin A (free) (synthetic)** [*Ent*-(*S*)-**1**]: $[\alpha]_D^{25}$ +70.4° (*c* 0.94, MeOH), $[\alpha]_D^{25}$ +79.2° (c 0.12, MeOH); (*S*)-(+)-Nakadomarin A (2HCl) (synthetic): $[\alpha]_D^{25}$ +45.0° (*c*

0.13, MeOH); [[α]$_D^{25}$ −16° (*c* 0.12, MeOH) [1a], [α]$_D$ −13° (*c* 0.12, $CHCl_3$) [1c]]. Optical purity of **1** was confirmed by HPLC analysis using a chiral column. A racemic form of **1** was subjected to HPLC analysis (column: Chiralcel OD column, 4.6 i. d. X 250 mm (three times), Daicel Chemical Ind., Ltd.; eluent *n*-hexane/2-propanol, 98:2; flow rate, 0.3 mL/min; temperature, 25 °C; detector, 206 nm) and peaks due to (*R*)-(-)-and *ent*-(*S*)-(+)-**1** were detected at t_R 36.0 and 41.0 min.

主論文目録

本学位論文の内容は下記の発表論文による。

主論文

1. Toshiaki Nagata, Atsushi Nishida, Masako Nakagawa
   Synthetic approach towards nakadomarin A:
   efficient synthesis of the central tetracyclic core
   Tetrahedron Letters, 42, 8345-8349 (2001).

副論文

1. Toshiaki Nagata, Yuuki Koide, Kazumasa Nara, Etsuko Itoh, Mistuhiro Arisawa, Shunji Naruto, Yasuhiro Torisawa, Tohru Hino, and Masako Nakagawa
   Lewis acid catalyzed Diels-Alder reaction of 3-phenylthio-2-quinolinones with siloxydiene. Synthesis of the intermediate for Dynemicin A core
   Chem Pharm. Bull. *44* (2) 451-453 (1996).

2. Yasuhiro Torisawa, Masako Nakagawa, Hideo Takami, Toshiaki Nagata, Mohamed Ayman Ali, and Tohru Hino
   Diels-Alder reaction of the N-protected 3-phenylthio-2(1H)-dihydropyridinone derivatives
   Heterocycles, *39* (1), 277-292 (1994)

3. Masamichi Yamanaka, Toshiaki Nagata, Yoshino Nakajima, Atsushi Nishida, and Masako Nakagawa
   Studies on the Asymmetric Diels-Alder reaction of dihydropyridin-2-one with siloxydiene
   Heterocycles, *56* (1), 283-290 (2002)

学会発表

1) 西田 篤司, ○長田 敏明, 狩野 琢哉, 小野 宏司, 有澤 光弘, 中川 昌子
29【PA】Ⅱ-069, ナカドマリンA全合成へのアプローチ
日本薬学会 第121年会(札幌) 要旨集2, p 78 (2001)

2) ○ Masako Nakagawa, Hideharu Uchida, Mariko Yamabe, Takeshi Watanabe, Kouji Ono, Keisuke Hatakeyama, Takuya Kano, Masakatsu Akiba, Toshiaki Nagata, and Atsushi Nishida;
OR7, Synthetic studies to Manzamine A, Manzamine B, and Nakadomarin A
10th International Symposium on Marine Natural Products(X MaNaPro)
Nago, Okinawa June 24-29, p45 (2001).

3) ○西田 篤司, 長田 敏明, 狩野 琢哉, 小野 宏司, 中川 昌子
P-61, ナカドマリンAの合成研究; Synthetic Study of Nakadomarin A
第43回 天然有機化合物討論会(大阪) 要旨集 105 (2001),

4) ○西田 篤司, 長田 敏明, 狩野 琢哉, 小野 宏司, 中川 昌子
1P-05, ナカドマリンAの合成研究
第27回 反応と合成の進歩シンポジウム (仙台) p 26 (2001)

5) 西田 篤司, 長田 敏明, ○狩野 琢哉, 中川 昌子
28【P】I-011, 海綿由来マリンアルカロイド、ナカドマリンAの全合成研究
日本薬学会 第122年会 (千葉) 要旨集2 p 70 (2002).

6) ○Masako Nakagawa, Toshiaki Nagata, Kouji Ono, Hideharu Uchida, Takeshi Watanabe, Takuya Kano, Masakatsu Akiba, Mitsuhiro Arisawa and Atsushi Nishida;ISTRY (International Study group for Tryptophan reserch)
L47 Reacent Development in Marine Indole Alkaloids Synthesis.
10th International Meeting on Tryptophan Research June 27-30, p 72 (2002)
Padova, Itary :

7) 長田 敏明, 小野 宏司, 狩野 琢哉, 中川 昌子, ○西田 篤司
105(P-61) 海洋産アルカロイド、ナカドマリンAの全合成研究
第44回 天然有機化合物討論会(東京) 要旨集 p 79-84 (2002).

8) ○長田 敏明, 小野 宏司, 狩野 琢哉, 中川 昌子, 西田 篤司
1-10 ナカドマリンAの全合成研究
第82回 有機合成シンポジウム講演要旨集 p45 (2002)

本学位論文の審査は千葉大学大学院薬学研究院で指名された下記の審査委員により行われた。

主査 千葉大学大学教授 (薬学研究院) 薬学博士 西田 篤司

副査 千葉大学大学教授 (薬学研究院) 薬学博士 濱田 康正

副査 千葉大学大学教授 (薬学研究院) 薬学博士 石川 勉

副査 千葉大学大学教授 (薬学研究院) 薬学博士 石橋 正己

副査 千葉大学大学助教授 (薬学研究院) 薬学博士 高山 廣光

謝辞

本研究に際し、終始御指導御鞭撻を賜りました恩師 西田 篤司 教授, 中川 昌子 前千葉大学薬学部教授, 日野 亨 千葉大学名誉教授, 荒井 秀 助教授に心から御礼申し上げます。

またこのような機会を下さいました武田薬品工業株式会社 常務取締役 (製薬本部長) 中村 省三 氏, 製薬研究所 所長 吉田 幸吉 博士, リサーチマネージャー 光寺 弘幸 博士, リサーチマネージャー 冨松 公典 博士, 事務課長 田中 正流 氏, 主席研究員 多和田 紘之 博士, 主席研究員 山野 光久 修士, 主任研究員 水谷 久 氏に感謝いたします。

また有益な御助言、御討論を賜りました有澤 光弘 博士, 内田 秀弘 博士, 主任研究員 福岡 孝一郎 博士に心から御礼申し上げます。

単結晶X線解析を測定してくださいました山口 健太郎 博士に厚く御礼申し上げます。また各種マススペクトルを測定してくださいました本学分析センター 関 弘子 博士, 原 律子 女史; 武田分析研究所 村林 秀樹 課長代理(医薬研究業務室付), 安田 行伸 主任研究員(元 武田薬品工業株式会社 製薬研究所 主席研究員), 医薬研究業務室 岩本 徹 氏, 試験第2部 小島 明美 女史 に感謝いたします。

実験の一部にご協力いただいた、小野 宏司 修士, 狩野 琢哉 修士に心より感謝いたします。

その他にも大勢の方の協力があり、本合成を達成できました。心から感謝いたします。

最後に、生活を支えてくれた妻 桜子に感謝いたします。

2003年3月　長田 敏明