

平成 25 年度
博士学位論文

カンプトテシン誘導体の
新規合成法の開発

Development of a Synthetic Route to
Camptothecin and its Analogues

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略語表

APCI	atmospheric-pressure chemical ionization
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
<i>c</i>	cyclo
calcd	calculated
cat	catalyst
Cbz	carbobenzyloxy
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
de	diastereomeric excess
ee	enantiomeric excess
eq	equivalent
Et	ethyl
ESI	electrospray ionization
FAB	fast atom bombardment
h	hour(s)
HRMS	high-resolution mass spectroscopy
HPLC	high-performance liquid chromatography
<i>i</i>	<i>iso</i>
IR	infrared
Me	methyl
min	minute(s)
mp	melting point
MS	molecular sieves
<i>m</i>	<i>meta</i>
<i>m/z</i>	mass to charge rate
<i>n</i>	normal
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
Pr	propyl
py	pyridine
rt	room temperature
SAR	structure-activity relationship
sat	saturated
<i>t</i>	<i>tertiary</i>
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl

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第1章

諸言・背景

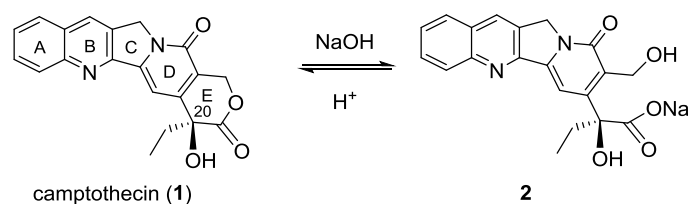
1-1 諸言

キラル化合物の医薬品開発において、必要な鏡像異性体のみを取得することは、重要な課題である。その第一の理由は、化合物の鏡像異性体間で、薬理作用、薬物動態、もしくは毒性プロファイルが異なるからである。これは、薬の作用する受容体や酵素などの生体内分子はキラルであるため、化合物の鏡像異性間でターゲット分子との相互作用に差異が生ずることにより引き起こされる。第二の理由として、開発の時間とコストの節約があげられる。thalidomide 薬害事件を契機に、薬物をラセミ体で使用する危険性が指摘されるようになり、FDA (Food and Drug Administration, 米国食品医薬品局) が、ラセミ体を開発する場合には両鏡像異性体の薬理作用、毒性、薬物動態などの試験結果を求めるようになった。つまり、片方の鏡像異性体の開発の方が、ラセミ体に比較して申請に必要なデータが半分で済むことになる。このように、医薬品の開発において、目的の鏡像異性体の取得は、科学的、かつ開発コスト的に重要な課題である。そして、医薬品候補化合物の合成を担う創薬化学者の役割は極めて大きい。

抗腫瘍性アルカロイドであるカンプトテシン (CPT, **1**)^[1]は、優れた抗腫瘍活性を示すことから医薬品の端緒化合物として注目されている。CPT 誘導体の合成における重要課題の一つは、活性発現に必須な C20 位不斉炭素の構築にある。これまでに様々な CPT C20 位不斉炭素構築法が報告されているが、収率、立体選択性、試薬の安全性、もしくは反応条件等に改善の余地があった。そこで、著者は CPT 誘導体の効率的合成法の確立を目的に、鍵ステップである C20 位不斉炭素の構築法を開発することとした。

1-2 カンプトテシン

カンプトテシン (CPT, **1**)は、1966 年、M. E. Wall らによって中国原産の植物 *Camptotheca acuminata* (ヌマミズキ科の喬木、喜樹)から単離されたアルカロイドである^[1]。CPT は、キノリン部から E 環部ラクトンまでの五環からなる変形モノテルペノイドインドールアルカロイドに分類され、E 環ラクトン部の C20 位に、S-配置の 3 級水酸基を有している (Scheme 1-1)。また、CPT の物理化学的特徴として、水溶性が極めて低いこと、および、分子内キノリン窒素の塩基性が低いために、塩酸等の鉱酸と水溶性塩を形成しないことが挙げられる。CPT は、マウスおよびラットの実験移植腫瘍系に対し顕著な抗腫瘍活性を示すことから注目を集め、1970 年代前半には、米国国立ガン研究所 (NCI)により消化器腫瘍、およびメラノーマを対象とした臨床試験が実施された。この際、CPT の難水溶性を改善する手段として、E 環部ラクトンを水酸化ナトリウムにより開環した水溶性の Na 塩 **2** (Scheme 1-1)が被験薬として用いられた。しかし、臨床試験では、期待された抗腫瘍効果が得られず、骨髄抑制、消化管障害、あるいは出血性膀胱炎などの重篤な副作用が発現したために CPT の開発は中止された^[2]。1966 年に構造が明らかとなって以来、CPT の全合成研究と共に、誘導体化研究が数多く行われたが、医薬品となり得る化合物の取得は困難を極めた。



Scheme 1-1. Structures of camptothecin (**1**) and its water-soluble sodium salt **2**.

1985 年、CPT の抗腫瘍効果は、新規メカニズムである I 型 DNA トポイソメラーゼ (トポ I) の阻害に基づくことが明らかとなった^[3]。トポ I は、大腸がん、腎がん、卵巣がん、

食道がん等の腫瘍組織で発現と酵素活性が顕著に上昇していることから^[4]、抗腫瘍薬開発の有望なターゲット分子と考えられる。CPTは、トポI阻害剤の端緒化合物として再び注目を集め、難水溶性の改善を志向した誘導体化研究が活発に行われることとなった^[5]。構造活性相関研究の結果、C20位のS-配置3級水酸基を含むE環ラクトン部、およびD環ピリドン部が抗腫瘍活性発現に必須であること、また、C7、C9、C10、もしくはC11位への置換基導入により、活性増強と溶解性改善を行えることが明らかとなった^[6] (Figure 1-1)。これまでに複数の水溶性CPT誘導体が合成され、抗腫瘍効果が検討された結果、irinotecan (3)^[7]、およびtopotecan (4)^[8]が、医薬品として臨床応用されるに至っている (Figure 1-2)。

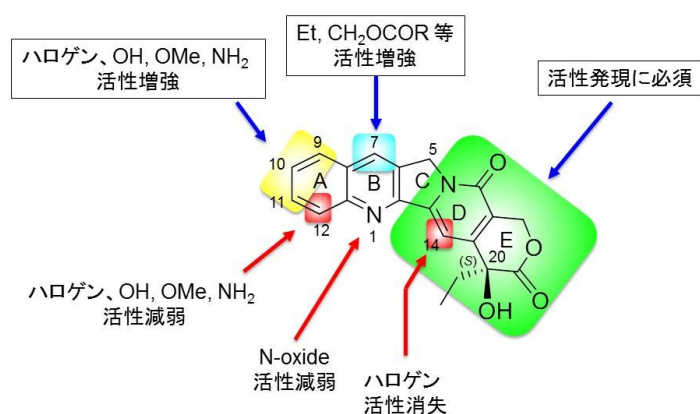


Figure 1-1. SAR of camptothecin derivatives.

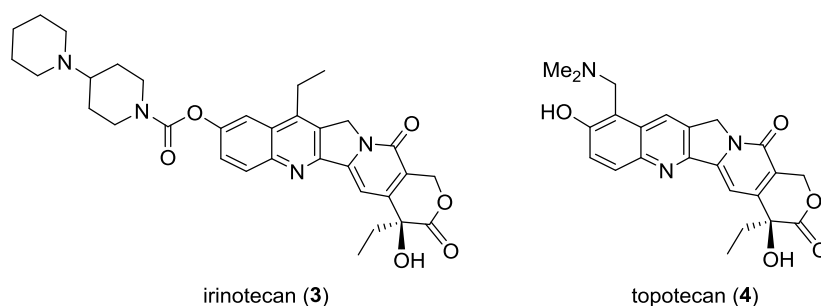


Figure 1-2. Structures of irinotecan (3) and topotecan (4).

1-3 水溶性カンプトテシン誘導体 T-2513 (5)

T-2513 (5) (Figure 1-3) は、田辺製薬(現・田辺三菱製薬)の研究グループが創製した水溶性 CPT 誘導体であり、C7 位にエチル基、C10 位に水溶性側鎖である 1-アミノプロピルオキシ基を有している。T-2513 (5)は、Walker-256 carcinoma 移植ラットに対して irinotecan (3)、topotecan (4)と同程度の抗腫瘍効果を示す。さらに、高分子複合体 T-0128 (6) (Figure 1-3)へ誘導することにより、極めて高い治療係数の獲得に成功している (Table 1-1)^[9]。

T-0128 (6) は、カルボキシメチルデキストラン(高分子キャリア)、トリグリシン(ペプチドスペーサー)、および T-2513 (5)(抗腫瘍化合物)がアミド結合を介して連結した構造を有している。各部分はそれぞれ、血中滞留性と腫瘍集積性の向上^[10]、腫瘍近傍での T-2513 (5)の放出、および殺細胞効果の役割を担い、腫瘍組織選択的な殺細胞効果を発揮していると考えられる。

以上のように、T-2513 (5)は抗腫瘍性化合物として優れたプロファイルを有する。

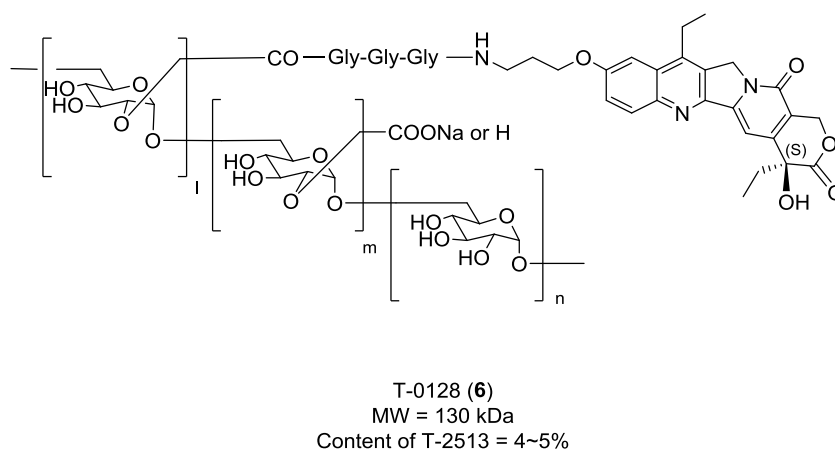
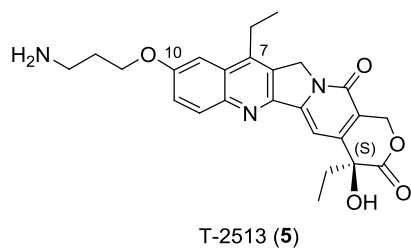


Figure 1-3. Structures of T-2513 (5) and T-0128 (6).

Table 1-1. Therapeutic index of CPT derivatives 3, 4, 5, and 6 in rats bearing Walker-256 carcinoma.

Drug	ED ₅₀ (mg/kg)	MTD (mg/kg) ^[a]	Therapeutic index ^[b]
irinotecan (3)	57	80	1.4
topotecan (4)	5.4	25	4.6
T-2513 (5)	23	60	2.6
T-0128 (6)	2.3 ^[c]	100 ^[c]	43

[a] MTD was determined using healthy SD rats; [b] Therapeutic index was determined by dividing MTD by ED₅₀; [c] The dose of T-0128 (6) expressed as a dose equivalent to T-2513 (5).
MTD: maximum tolerated dose (最大耐性量)

1-4 他グループによる CPT、および CPT 誘導体の合成

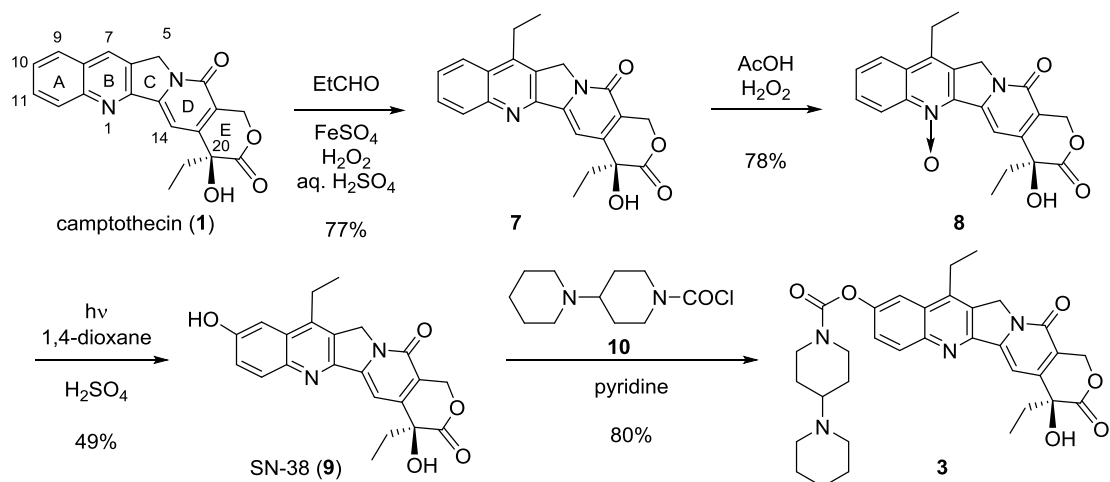
CPT の特異な縮環構造は、有機合成化学的に興味深いターゲットであることから、これまでに多様な合成が報告されている^[5a,5b,11,12]。以下に、創薬研究の上で特に重要な合成法について、その特徴をまとめる。

1-4-1 CPT からの半合成

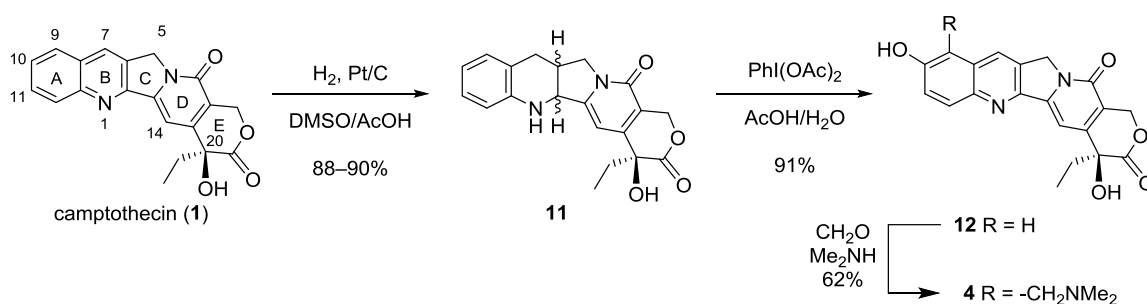
医薬品として使用されている irinotecan (**3**)、および topotecan (**4**)は、*Nothapodytes foetida* (クロタキカズラ科クサミズキ)^[13]から抽出される CPT(**1**)より半合成されている (Schemes 1-2 and 1-3)。半合成の最大の利点は、最小限の化学変換により irinotecan (**3**)、および topotecan (**4**)へと誘導できることである。一方、問題点としては、原料のクサミズキが絶滅危惧種に指定されている点、また、半合成で可能な化学変換が限定的である点があげられる。これらを考慮すると、多様な CPT 誘導体へと合成展開でき、かつ効率的な全合成法の開発は依然として必要性が高いと考えられる。

irinotecan (**3**)の半合成ルートを Scheme 1-2 に示した^[7c]。CPT (**1**)をラジカル条件下にエチル化し 7-ethylcamptothecin (**7**)を得る。**7** を *N*-oxide **8** へと酸化した後、1,4-dioxane 中で硫酸共存下に高圧水銀灯で光照射することにより 7-ethyl-10-hydroxycamptothecin (SN-38, **9**)を得る。次いで、**9** のフェノール性水酸基を **10** によりカルバモイル化することにより irinotecan (**3**)を得ることができる。

また、Scheme 1-3 には、topotecan (**4**)の半合成ルートを示した^[14]。CPT (**1**)を AcOH/DMSO 中で Pt/C 触媒下に接触還元し、テトラヒドロ体 **11** を 2 種類の異性体混合物として得る。**11** を AcOH/H₂O 中で PhI(OAc)₂ で酸化することにより 10-hydroxycamptothecin (**12**)へと誘導する。次いで、**12** を CH₂O/Me₂NH を用いてジメチルアミノメチル化して topotecan (**4**)を得ることができる。



Scheme 1-2. Semisynthesis of irinotecan (3) from CPT (1).



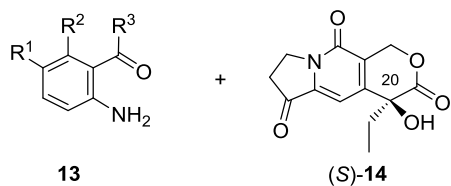
Scheme 1-3. Semisynthesis of topotecan (4) from CPT (1).

1-4-2 CPT および CPT 誘導体の全合成

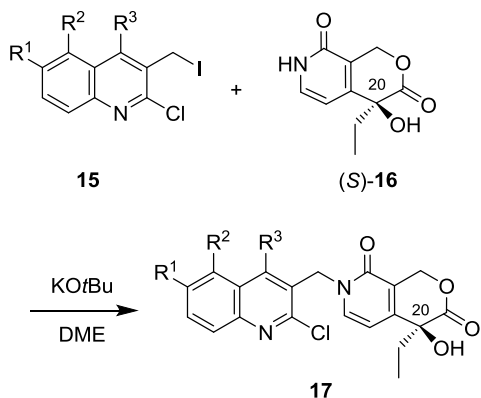
1-4-2-1 CPT 母核の構築

CPT の AB 環部構造修飾は、抗腫瘍活性増強と水溶性向上の双方に寄与することから (Fig 1-1 参照)、数多くの AB 環修飾 CPT 誘導体が報告されている。これらの誘導体に適用されている代表的な CPT 骨格構築法が、Friedlander 縮合法^[15]、Comins 法^[16]、および Curran 法^[17]の 3 種類である (Scheme 1-4)。

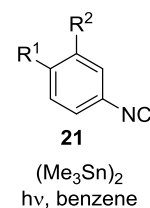
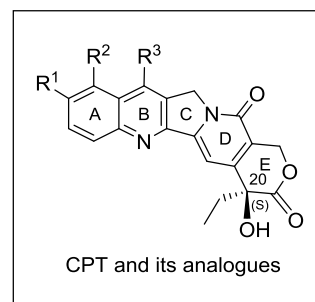
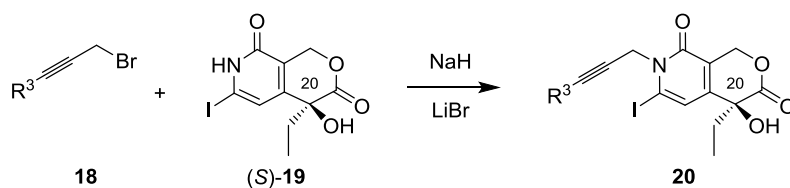
Friedlander condensation approach



Comins' approach



Curran's approach



Scheme 1-4. Construction of the CPT ring system.

Friedlander 縮合法は、三環性ケトン(S)-14 とアミノケトン **13** とを酸性条件下で縮合することにより、最終段階で CPT の B 環を構築するアプローチである。Comins 法は、縮環ピリドン誘導体 (Comins 中間体、(S)-16) の N-アルキル化により得られる **17** を、分子内 Heck 反応に付し、最終段階で CPT の C 環を構築するアプローチである。また、Curran 法は、ヨード置換縮環ピリドン誘導体 (Curran 中間体、(S)-19) を N-プロパギル化して **20** とした後、アリールイソニトリル **21** とラジカル環化を行うことにより、B-C 環を一気に構築するアプローチである。いずれの方法も、光学活性中間体(S)-14、

(*S*)-**16**、もしくは(*S*)-**19**に対して、A~B部を結合する収束的な合成法であるため、効率的にAB環修飾CPT誘導体を合成することができる。

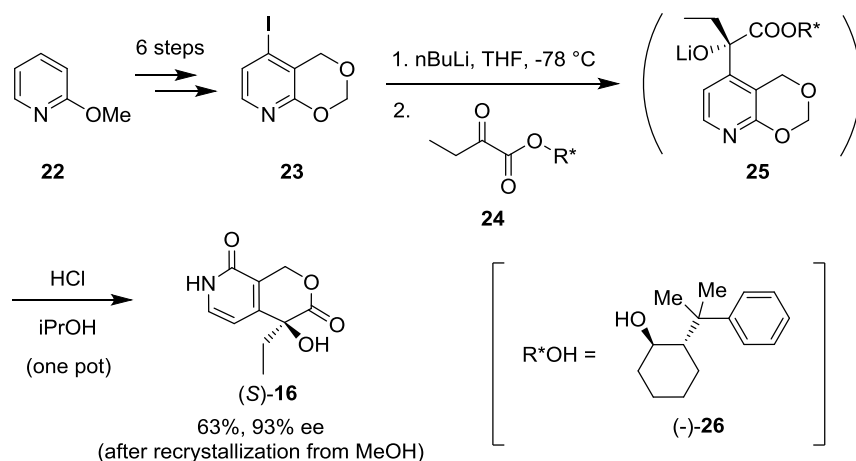
1-4-2-2 CPTのC20位不斉炭素の構築

CPTのC20位不斉炭素の構築法は、主に6種類の方法に分類することができる。すなわち不斉補助基を用いた立体選択的官能基導入、不斉ジオール化、不斉シアノヒドリン化、光学分割、酵素による非対称化、および不斉ヒドロキシ化である。以下にそれぞれの方法の特徴をまとめる。

1-4-2-2-1 不斉補助基を用いた立体選択的官能基導入

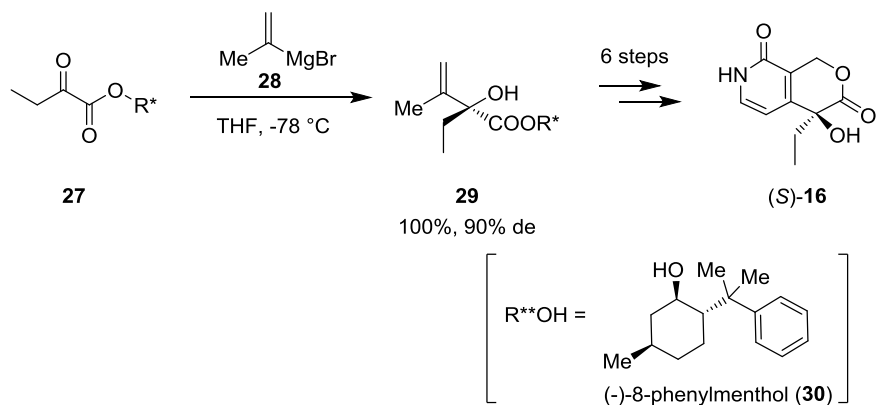
(i) キラル α -ケトエステルへのジアステレオ選択的1,2-付加反応

Cominsらは、キラルシクロヘキサノール(-)-**26**を不斉補助基に用いた中間体(*S*)-**16**の立体選択的合成を報告している。ヨード体**23**を-78℃の低温にてハロゲンリチウム交換後、キラル α -ケトエステル**24**へ高ジアステレオ選択的に1,2-付加させることにより**25**を合成する。次いで、**25**の脱アセタール化とラクトン化を行いComins中間体(*S*)-**16**(63%, 93% ee)へと誘導している(Scheme 1-5)^[16]。



Scheme 1-5. Diastereoselective synthesis of Comins' intermediate ((*S*)-**16**) by using (-)-**26** as a chiral auxiliary.

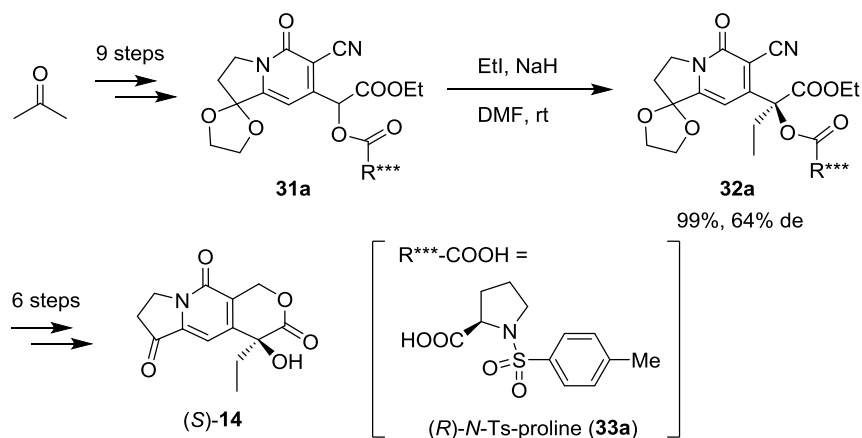
一方、Petersらは、(-)-8-phenylmenthol (**30**)を不斉補助基に用いた合成を行っている。キラル α -ケトエステル **27** に対して Grignard 試薬 **28** を -78 °C の低温にてジアステレオ選択的に 1,2-付加させ、アルコール **29** (100%、90% de)を得ている。さらに、**29** を 6 工程で Comins 中間体 (*S*)-**16** へと誘導している (Scheme 1-6)^[18]。



Scheme 1-6. Diastereoselective synthesis of Comins' intermediate ((*S*)-**16**) by using (-)-**30** as a chiral auxiliary.

(ii) キラル α -アシルオキシエステルのジアステレオ選択的アルキル化反応

Tagawaらは、(*R*)-*N*-Ts-proline (**33a**)を不斉補助基に用いた **31a** のジアステレオ選択的エチル化により **32a** (99%、64% de)を得ている。**32a** を再結晶により光学純度 100%とした後、6 工程で三環性ケトン(*S*)-**14** へと誘導している (Scheme 1-7)^[19]。

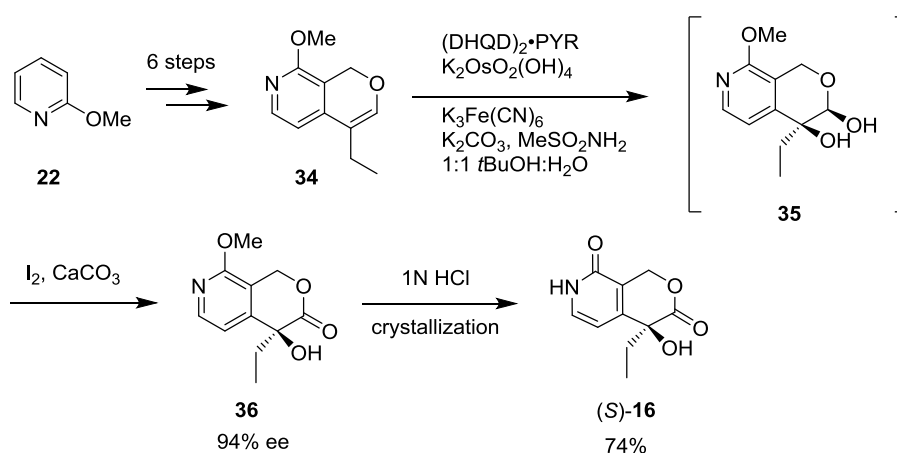


Scheme 1-7. Diastereoselective synthesis of tricyclic ketone (*S*)-**14** by using *N*-Ts-(*R*)-proline (**33a**) as a chiral auxiliary.

本反応の特長の一つは、反応温度を $-10\text{ }^{\circ}\text{C}$ 、もしくは $60\text{ }^{\circ}\text{C}$ にしてもエチル化の立体選択性が変化しない点にある。その理由は、**31** から生成するエノラートが、堅固なコンフォメーションを取っているためと考えられている。このように、Tagawa 法は、厳密に反応温度を制御しなくても、高い再現性で立体選択性を発現できるという特長を持つことから、大量合成に適用し易い合成法と考えられる。

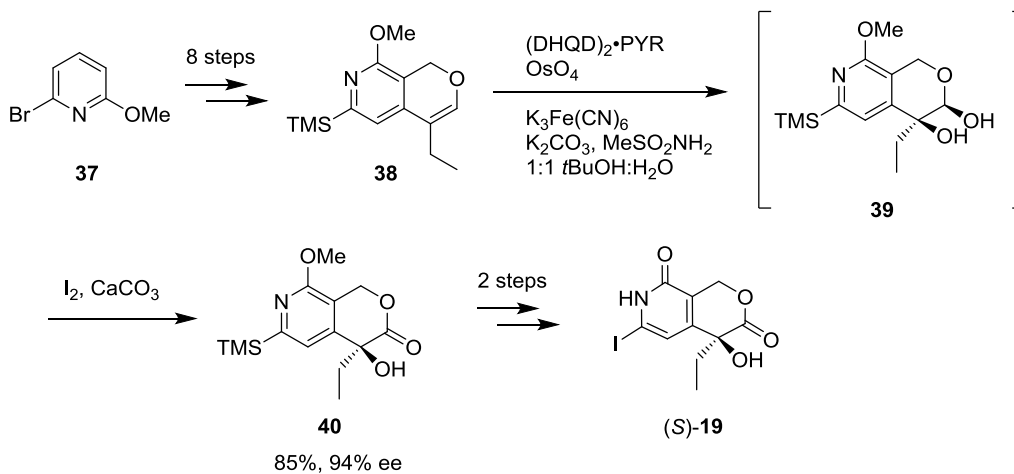
1-4-2-2 触媒的不斉ジオール化

Fangらは、2-methoxypyridine (**22**)から6工程で合成した環状エノールエーテル**34**を触媒的不斉ジオール化に付し、ヘミアセタール**35**とした後、酸化することによりラクトン**36**を94% eeで取得している。続いて、ラクトン**36**の脱メチル化を行い、Comins 中間体 (*S*)-**16**へと誘導している (Scheme 1-8)^[20]。



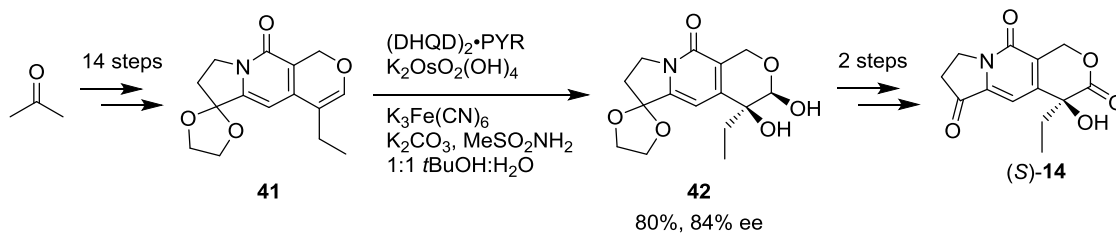
Scheme 1-8. Synthesis of Comins' intermediate ((*S*)-**16**) by using catalytic asymmetric dihydroxylation.

Curran らは、環状エノールエーテル **38** の触媒的不斉ジオール化と酸化により、ラクトン **40** を85%収率、94% eeで得ている。さらに、ラクトン **40** を2工程でCurran 中間体 (*S*)-**19**へと誘導している (Scheme 1-9)^[17]。



Scheme 1-9. Synthesis of Curran's intermediate ((*S*)-19) by using catalytic asymmetric dihydroxylation.

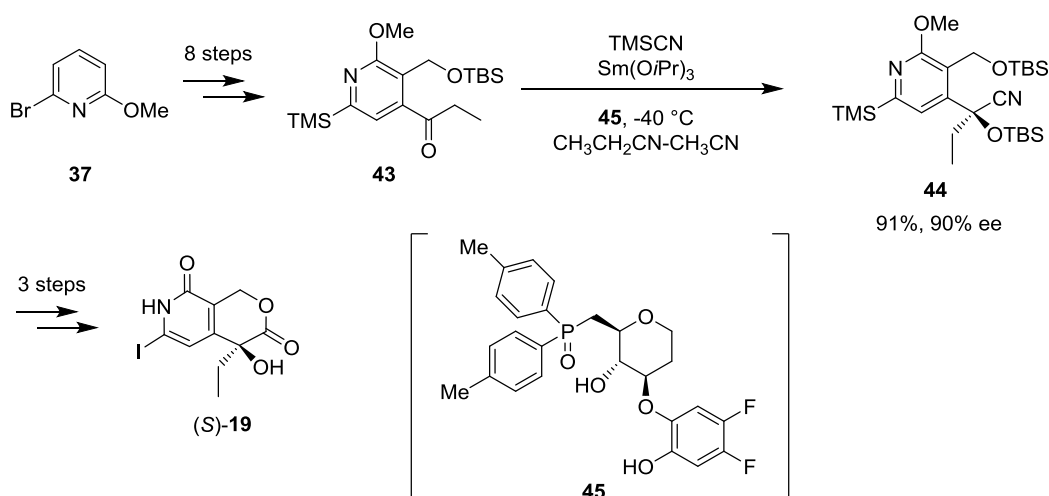
Jewらは、アセトンから14工程で合成した環状エノールエーテル **41** の触媒的不斉ジオール化によりヘミアセタール **42** を80%収率、84% eeで取得している。その後2工程で、三環性ケトン(*S*)-**14**へと誘導している (Scheme 1-10)^[21]。



Scheme 1-10. Synthesis of tricyclic ketone (*S*)-14 by using catalytic asymmetric dihydroxylation.

1-4-2-2-3 触媒的不斉シアノシリル化

ShibasakiらはD-glucose由来のキラルリガンド**45**とSmを用いた、ケトン**43**の触媒的不斉シアノシリル化によりシアノ体**44**を91%収率、90% eeで得ることに成功している。その後、**44**から3工程でCurran中間体(S)-**19**へと誘導している(Scheme 1-11)^[22]。

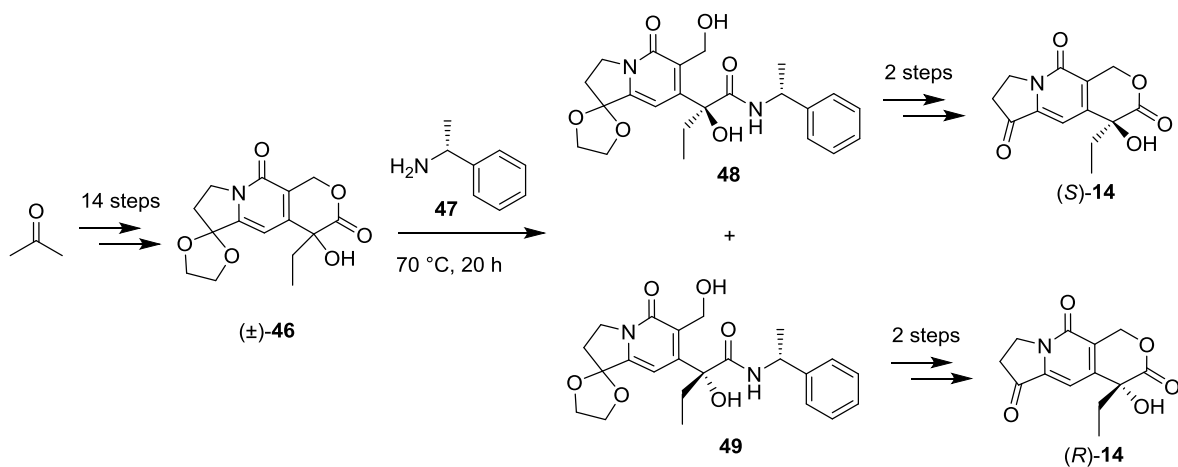


Scheme 1-11. Synthesis of Curran's intermediate ((S)-**19**) by using catalytic asymmetric cyanosilylation.

1-4-2-2-4 光学分割

(i) キラルアミンとのアミド形成による化学的分割

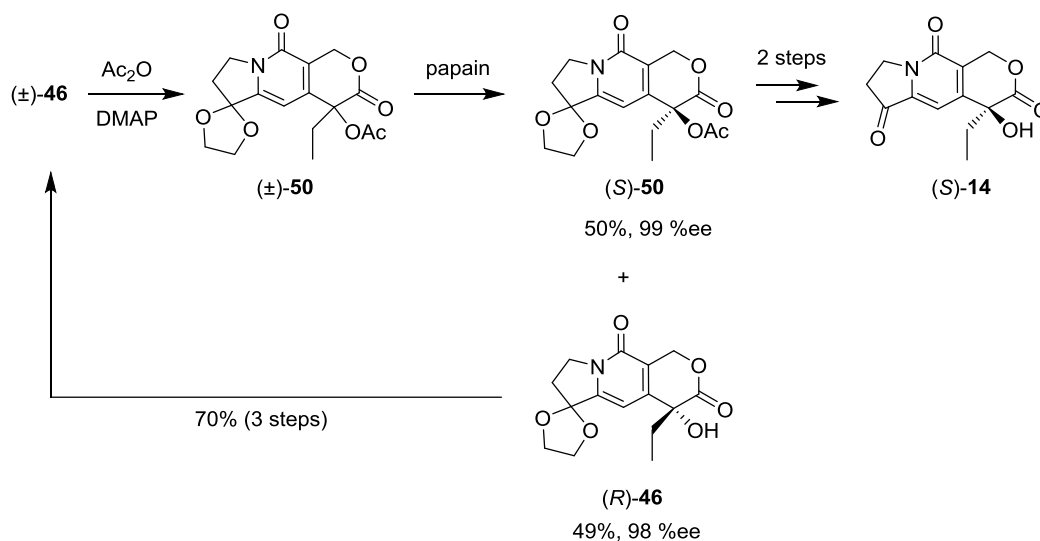
Waniらは、ラセミ体(±)-**46**とキラルアミン**47**とから、ジアステレオ異性体のアミド**48**および**49**を合成している。所望の絶対配置を有するアミド**48**を2工程で三環性ケトン**14**へと誘導している(Scheme 1-12)。また、Waniらは**49**から誘導した(R)-**14**を用いて非天然型の(20R)-CPTを合成している。天然型(20S)-CPT(**1**)と非天然型(20R)-CPTについて、培養細胞(9KB, ヒト鼻咽頭上皮癌; 9PS, マウス白血病)に対する殺細胞効果を比較した結果、天然型(20S)-CPT(**1**)が10から100倍程度高活性であることを明らかにしている^[23]。



Scheme 1-12. Resolution of (±)-46 by the separation of diastereomeric amide derivatives 48 and 49.

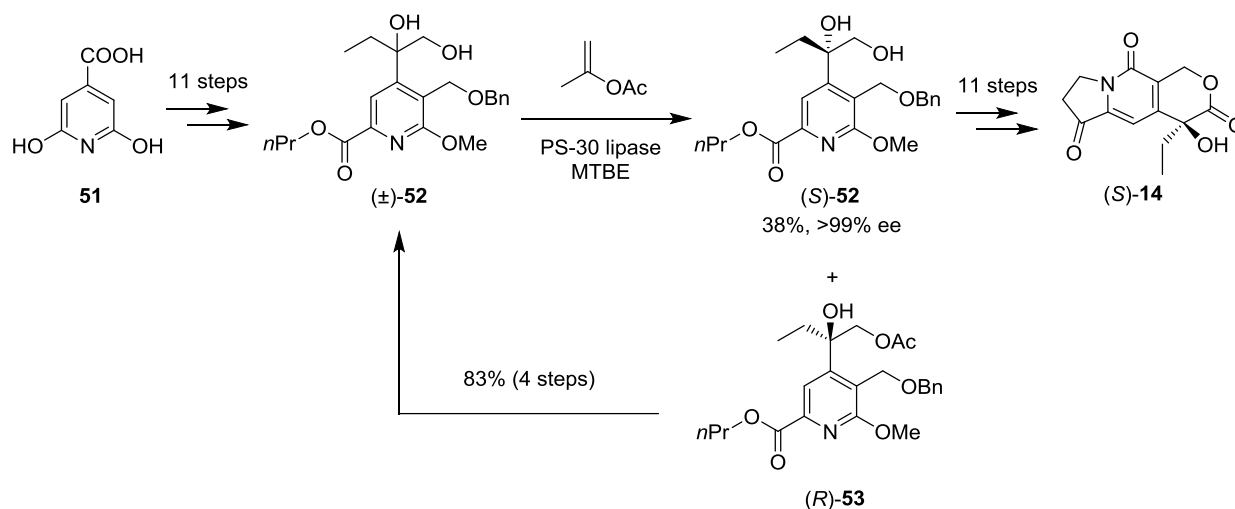
(ii) 酵素を用いた光学分割

Imura らは、ラセミ体(±)-46 の 3 級水酸基をアセチル化した(±)-50 を基質に用いて papain による酵素的光学分割を行っている。所望の絶対立体配置を有する(S)-50 から 2 工程で三環性ケトン(S)-14 を得ることができる。一方、対掌体である(R)-46 は、3 工程 70%収率でラセミ体 46 へと変換し、再利用することが可能である (Scheme 1-13)^[24]。



Scheme 1-13. Papain-catalyzed resolution of (±)-50.

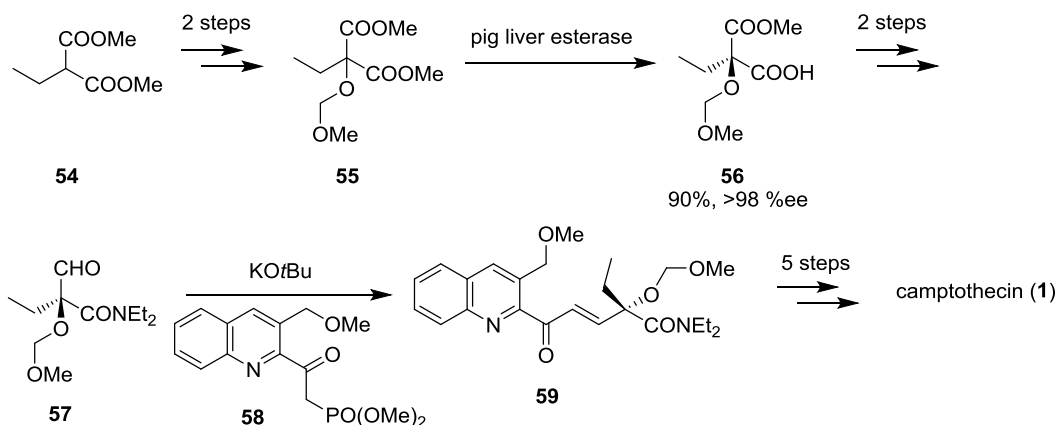
また、Henegarらは citrazinic acid (**51**)から 11 工程で合成したジオール(±)-**52** の酵素的光学分割を報告している。所望の絶対立体配置を有する(*S*)-**52** から 6 工程で三環性ケトン(*S*)-**14** を得ることができる。一方、対掌体である(*R*)-**53** は、4 工程 83%収率で(±)-**52** へと変換し、再利用することが可能である。本法を用いて 30 kg スケールの大量合成が行われている (Scheme 1-14)^[25]。



Scheme 1-14. Synthesis of tricyclic ketone (**14**) by using lipase-catalyzed resolution of (±)-**52**.

1-4-2-2-5 酵素による非対称化

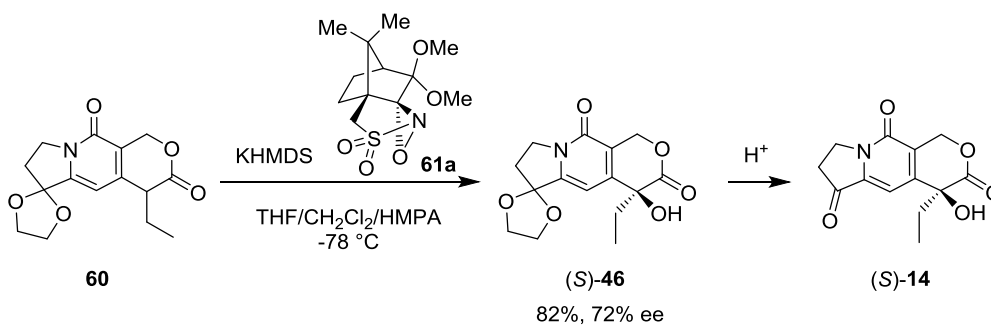
ラセミ体の光学分割の収率は、本質的に 50%を上回ることがない。この問題を解決する一つの方法が、対称化合物の非対称化である。Ciufolini らは、対称ジエステル **55** を、pig liver esterase を用いて加水分解することにより、キラルカルボン酸 **56** を 90% 収率、>98% ee で得ることに成功している。次いで、**56** を 2 工程でアルデヒド **57** へと変換し、A-B環部ユニット **58** との結合を経て、CPT の全合成を達成している (Scheme 1-15)^[26]。



Scheme 1-15. Synthesis of CPT (**1**) by using Ciufolini's enzymatic desymmetrization approach.

1-4-2-2-6 不斉ヒドロキシ化

Chenらは、ラクトン **60** の不斉ヒドロキシ化を検討し、キラルオキサジリジン **61a** を酸化剤に用いることによって、(*S*)-**46** を 82%収率、72% ee で得ている (Scheme 1-16)^[27]。

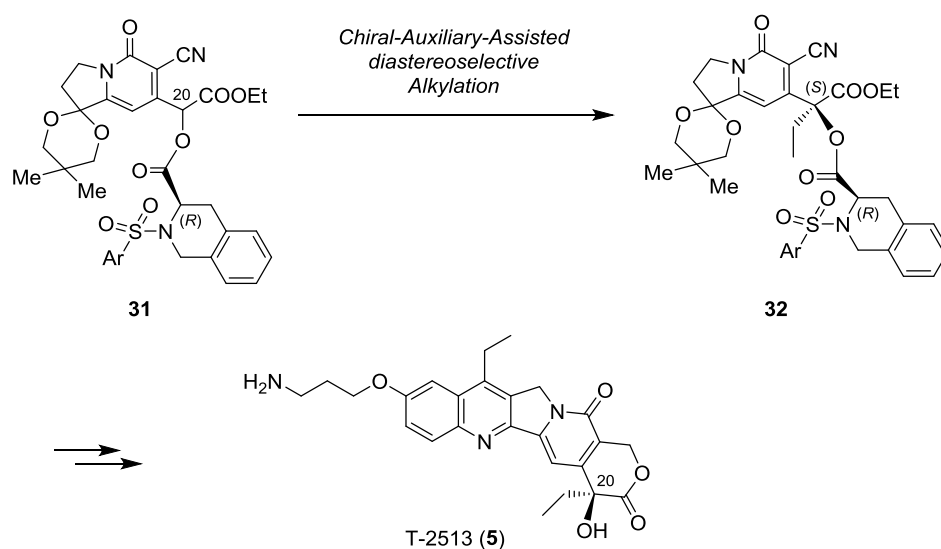


Scheme 1-16. Asymmetric hydroxylation of **60** by using chiral oxaziridine **61** as an oxidant.

1-5 本研究の目的と意義

本研究の目的は、抗腫瘍薬として有用な CPT 誘導体の効率的な新規不斉合成法を開発し、実用に供することにある。

第 2 章では、水溶性 CPT 誘導体 T-2513 (**5**)の実用的合成法の開発について述べる。著者は、創薬研究における各種評価用サンプルの円滑な供給を目的に、また将来の工業スケール合成への適用を指向して合成法の検討を行った結果、中間体 **32** の高立体選択的合成に成功した。さらに、この反応を鍵反応に用いて大量合成に適用可能な **5** の実用的全合成法を確立した。



Scheme 1-17. A key step for the synthesis of T-2513 (**5**).

第 3 章では、CPT、および CPT 誘導体の鍵合成中間体(*S*)-**46** の触媒的不斉合成について述べる。著者はグアニジン-ウレア **62** が、中間体 **60** の不斉ヒドロキシ化の触媒に適用できることを見出した。さらに、**62** の構造を最適化することにより、中間体 (*S*)-**46** の高エナンチオ選択的合成を達成した。本反応は、安価で大量に購入できる

第2章

水溶性カンプトテシン誘導体 T-2513 の実用的合成法の開発

2-1 諸言

水溶性 CPT 誘導体 T-2513 (**5**)は、抗腫瘍性化合物として優れたプロファイルを有する(第1章3項)。著者は、高次の薬理試験、薬物動態試験、および安全性試験実施のためのサンプル供給を目的に、また将来の工業スケール合成への適用を指向して、T-2513 (**5**)の実用的合成法の開発に取り組むこととした。研究に着手するにあたり、著者が設定した実用的合成法の必要条件は下記3項目である。

- ◆ カラムクロマトグラフィー精製を必要としない。
- ◆ 毒性・危険性の高い試薬の使用が最小限に抑えられている。
- ◆ 極低温等の過酷な反応条件を必要としない。

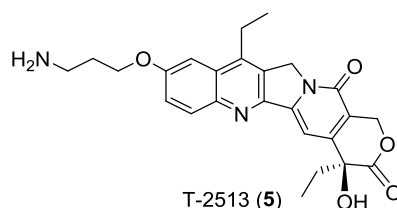


Figure 2-1. Structure of T-2513 (**5**).

2-2 合成計画

第1章4-2-1にまとめた通り、CPT母核構築の代表的な方法として、Friedlander縮合法、Comins法、およびCurran法が報告されている(Schemes 1-4 and 2-1)。著者は、これらの中からFriedlander縮合法をT-2513 (**5**)の実用的合成に適用することとした。その理由として2点をあげることができる。第1の理由は、探索研究における各種CPT誘導体の合成にFriedlander縮合法を利用していたため、反応の操作性や中間体の

密な反応温度制御を必要としないためである。CPT の C20 位不斉炭素構築法の多くは、毒性の高い試薬 (OsO_4)を使用する点 (Schemes 1-8, 1-9, and 1-10) や、立体選択性発現のため低温反応を必要とする点 (Schemes 1-5, 1-6, 1-11, and 1-16) で実用面に課題を持つのに対して、Tagawa 法は実用性の高い特長を備えている。

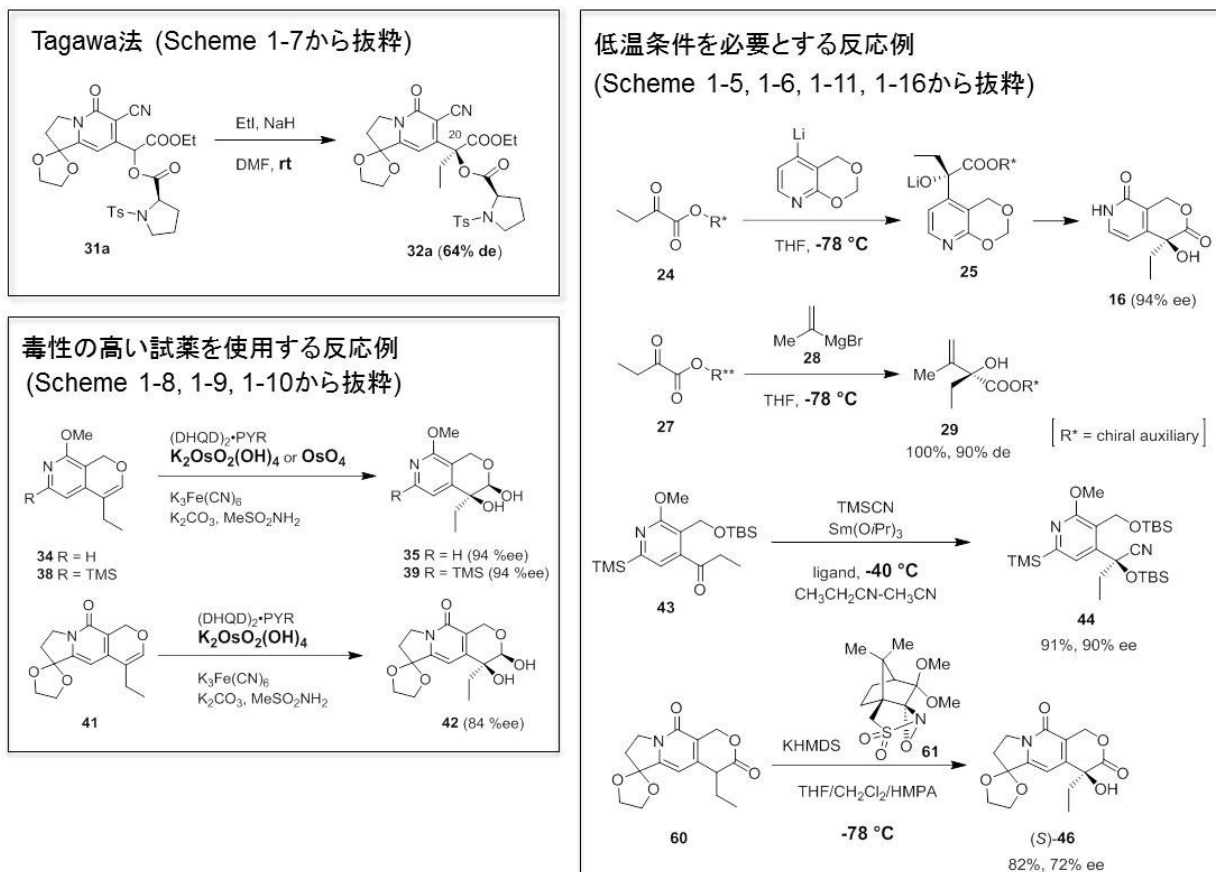
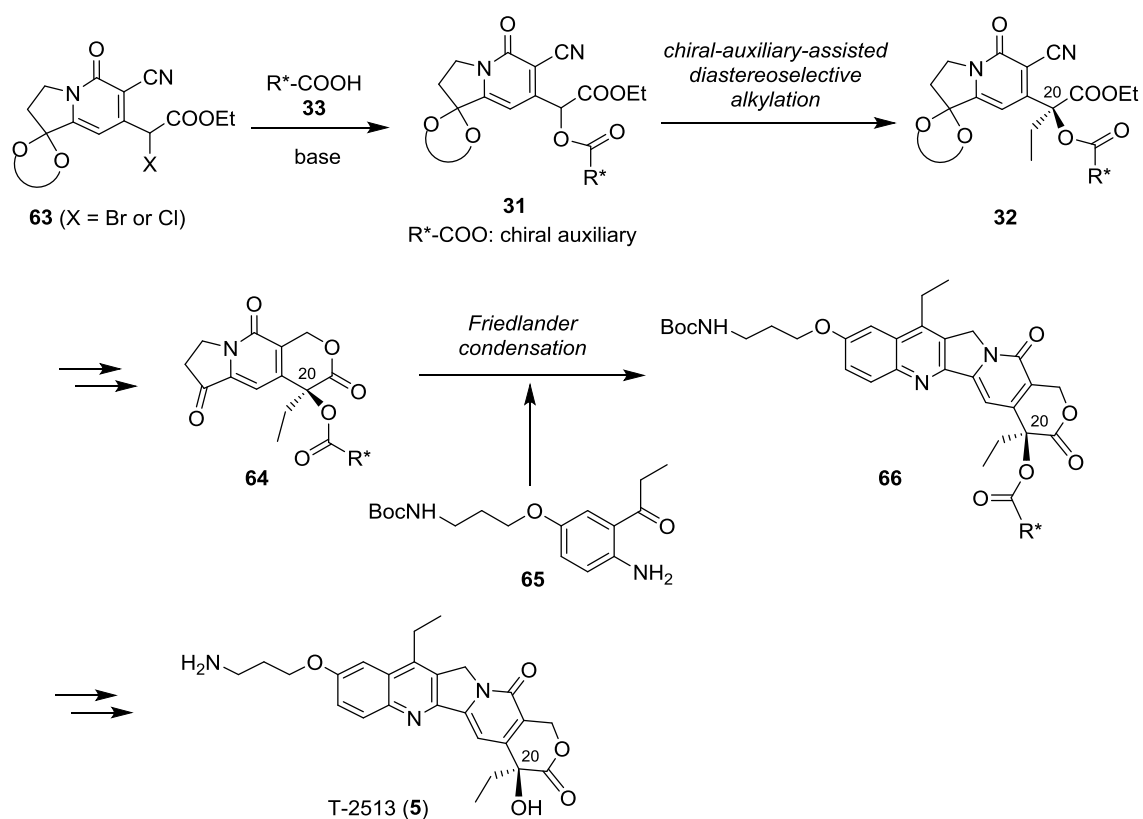


Figure 2-2. Reaction conditions for construction of the stereogenic center at the C20 position of CPT.

第 2 の理由は、Tagawa 法には、反応の立体選択性に改善の余地があると判断したからである。Tagawa らが検討した不斉補助基は、6 種類の *N*-置換 proline 誘導体に限定されているため、検討範囲の拡大により *N*-Ts-(*R*)-proline (**33a**)を凌駕する新たな不斉補助基を発見する可能性は高いと考えた。

以上述べた点を踏まえて、T-2513 (**5**)の合成ルートを以下のように設定した (Scheme 2-2)。α-ハロエステル **63** に、不斉補助基として種々のキラルカルボン酸 **33** を反応させジエステル **31** を合成し、**31** のジアステレオ選択的エチル化を検討する。高いジアステレオ選択性で得た **32** について、可能基変換を行い三環性ケトン **64** へと誘導する。三環性ケトン **64** と、別途合成したアミノケトン **65** との Friedlander 縮合により、CPT 誘導体 **66** へと誘導する。最終段階として、**66** の脱保護を行い T-2513 (**5**)の合成を行う。

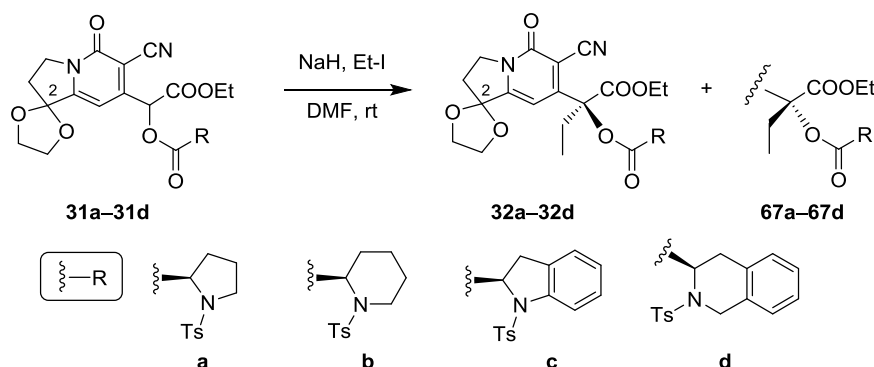


Scheme 2-2. Key features of the synthesis of T-2513 (**5**).

2-3 ジアステレオ選択的エチル化反応の開発

Tagawa らは 20(*S*)-CPT の合成において、(*R*)-*N*-Ts-proline ester **31a** のジアステレオ選択的エチル化を報告しているが、選択性は 64% de にとどまっていた (Table 2-1, entry 1)^[19]。著者は、より効果的な不斉補助基を見出すべく、*N*-Ts-環状アミノ酸誘導体 **31b–31d**^[28] を Tagawa らの反応条件下にエチル化し、環サイズ、および、縮環様式が、ジアステレオ選択性に及ぼす影響を評価した (Table 2-1)。なお、初期検討では、エチル化のジアステレオ選択性の確認を最優先課題に据え、不斉補助基の *N*-置換-環状アミノ酸 **33**^[29] は、入手容易なラセミ体を用いて検討を行った。

Table 2-1. Diastereoselective ethylation of **31a–31d** bearing a *N*-tosyl-cyclic amino acid ester as chiral auxiliaries.^[a]



Entry	31	32+67		
		Yield (%) ^[b]	Ratio 32/67 ^[c]	de (%)
1	a	99	82:18	64
2	b	82	86.5:13.5	73
3	c	90	76.5:23.5	53
4	d	93	89:11	78

[a] Reactions were performed with **31** (1.2 mmol), NaH (1.4 mmol), and EtI (12 mmol) in DMF at room temperature under an argon atmosphere. [b] Yields of the diastereoisomers (**32** and **67**). [c] Determined by ¹H NMR analysis of the mixture of **32** and **67**.

6 員環アミン部を有するピペコリン酸エステル **31b**、およびテトラヒドロイソキノリンカルボン酸(TIC)エステル **31d** においてジアステレオ選択性が各 73% de、および 78%

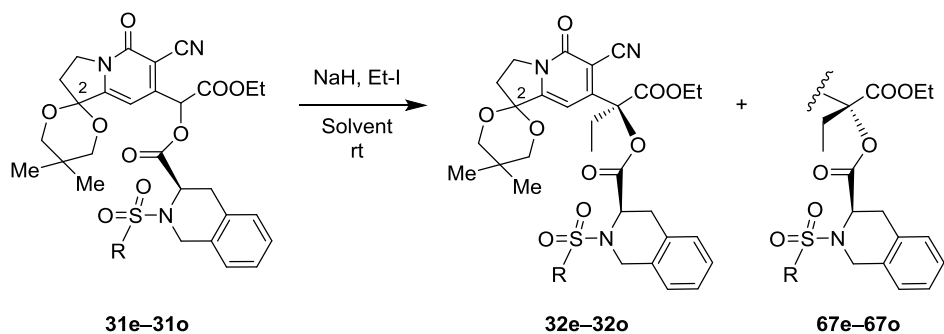
de に向上することを見出した (Table 2-1, entries 2 and 4)。一方、5 員環アミン部を有するインドリン-2-カルボン酸エステル **31c** では、**31a** に比較してジアステレオ選択性が大幅に低下することがわかった (Table 2-1, entry 3)。これらの結果から、5 員環アミンよりも 6 員環アミンに置換した Ts 基が、より効果的に **31** から生ずるエノレート平面を遮蔽すると考えられる。

また、C2 位の環状アセタール部はエチレンアセタール **31d** (Table 2-1, entry 4) からネオペンチルグリコールアセタール **31e** (Table 2-2, entry 1) へと変換しても、エチル化の選択性に大きな影響を及ぼさないことがわかった (各 78%、および 77% de)。C2 位ケトンの環状アセタール化は、ネオペンチルグリコールアセタール化の方が高収率で進行する点を考慮して^[30]、以降の検討は C2 位ネオペンチルグリコールアセタール体を用いることにした。

次に、TIC エステル **31e** の *N*-Ts-部を他のアリアル (またはアルキル) スルホンアミドで置き換えた **31f-31o** を用いて、ジアステレオ選択的エチル化を検討した (Table 2-2)。 **31e** の Ts 部ベンゼン環の電子的環境が選択性に与える影響を確認するために、電子求引性の **31f** (4-Cl-phenyl)、および、電子供与性の **31g** (4-MeO-phenyl) を用いてエチル化を行った。TIC エステル **31f**、**31g** ともに **31e** に比較して選択性は向上し、電子求引性の **31f** の方が **31g** より若干高い選択性を示した (Table 2-2, entries 2 and 3)。立体的に嵩高い置換基へと変換したところ (**31h**, 4-PhO-phenyl; **31i**, 4-*t*Bu-phenyl; **31j**, 4-cyclohexylphenyl)、いずれも 80% de 程度の選択性を示した (Table 2-2, entries 4-6)。さらに検討した結果、4-biphenyl 体 **31k** では選択性が 84% de に向上することを見出した (Table 2-2, entry 7)。4-biphenyl 体 **31k** について、反応溶媒を DMF から *N,N*-dimethylacetamide (DMAc) に替えると、選択性は 86% de へと向上した (Table 2-2, entry 8)。さらに、DMAc-トルエン (1:1 v/v) の混合溶媒を用いると、選択性は 87% de まで上昇することがわかった (Table 2-2, entry 9)。一方、naphthalen-2-yl 体 **31l**、naphthalen-1-yl 体 **31m**、もしくは indan-5-yl 体 **31n** のような縮環体では、それ

それぞれ 82%、75%、および 74% de の選択性を示した (Table 2-2, entries 10–12)。また、benzyl 体 **31o** では、選択性が 45% de へ大幅に低下した (Table 2-2, entry 13)。

Table 2-2. Diastereoselective ethylation of **31e–31o** having TIC esters as chiral auxiliaries.^[a]



Entry	31	R	Solvent	Yield (%) ^[b]	32
					de (%) ^[c]
1	e	4-Me-phenyl	DMF	94	77
2	f	4-Cl-phenyl	DMF	91	82
3	g	4-MeO-phenyl	DMF	92	80
4	h	4-PhO-phenyl	DMF	88	80
5	i	4- <i>t</i> -Bu-phenyl	DMF	90	79
6	j	4-cyclohexyl-phenyl	DMF	88	80
7	k	4-biphenyl	DMF	89	84
8	k	4-biphenyl	DMAc	87	86
9	k	4-biphenyl	DMAc/toluene (1/1)	93	87
10	l	naphthalen-2-yl	DMF	91	82
11	m	naphthalen-1-yl	DMF	91	75
12	n	indan-5-yl	DMF	90	74
13	o	benzyl	DMF	94	45

[a] Reactions were performed with **31** (1.2 mmol), NaH (1.4 mmol), and EtI (12 mmol) in the indicated solvent at room temperature under an argon atmosphere. [b] Yields of the diastereoisomers (**32** and **67**). [c] Determined by ¹H NMR analysis of the mixture of **32** and **67**.

エチル化の立体選択性発現の要因を、エステル体 **31a**、**31d**、および **31k** から生じるエノレートのコンフォメーションに着目して考察した (Figure 2-3)。

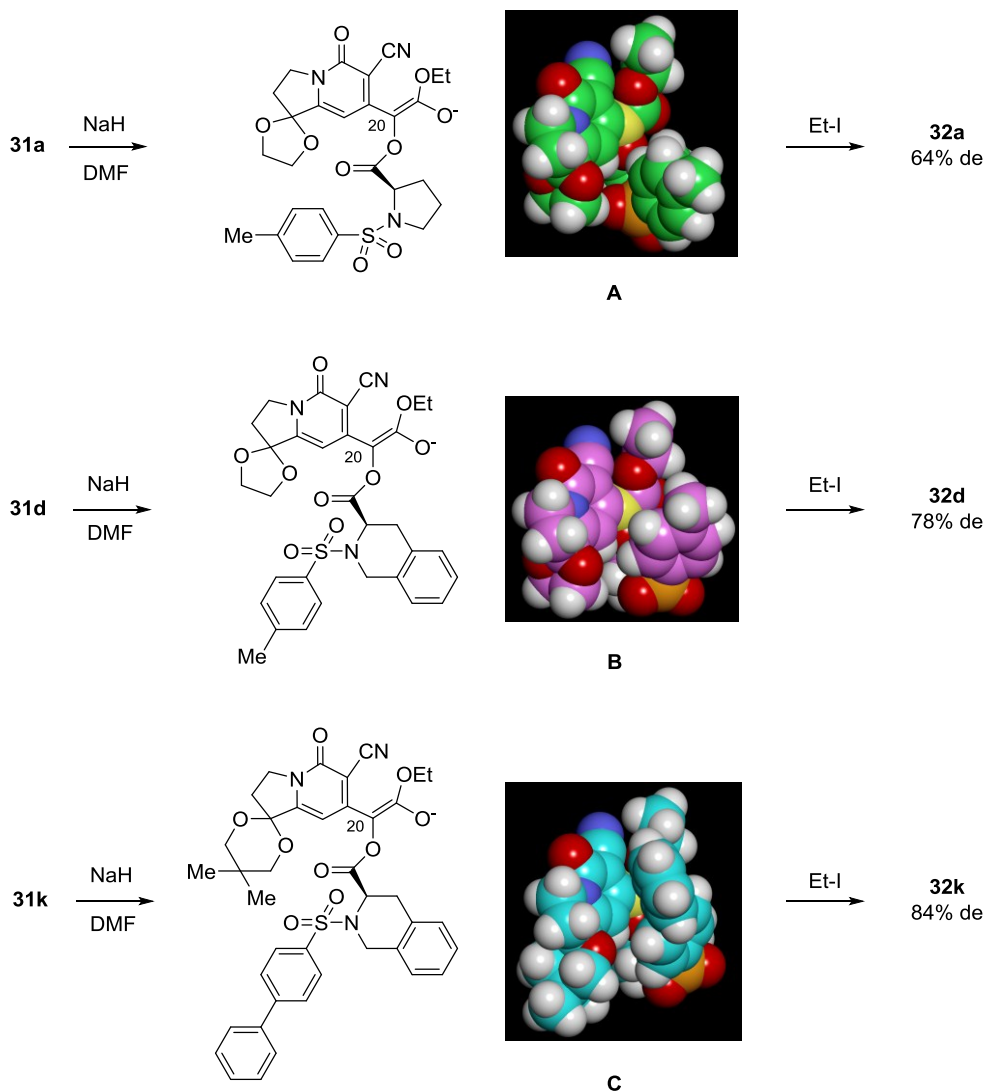


Figure 2-3. Plausible conformations of the enolate anions of compounds **31a**, **31d**, and **31k**; the C20 carbon atom is shown in yellow.

各エノレートの取り得る安定コンフォメーションを、Corey-Pauling-Koltung (CPK) モデル **A**、**B**、および **C** で表示し、C20 位炭素を黄色にハイライトした。コンフォメーション **A**、**B**、および **C** にて、アリールスルホニル基はエノレートの *Si*-面 (紙面手前側) を

遮蔽するため、iodoethane の接近は *Re*-面(紙面裏側)からが優先されると考えられる。また、アリールスルホニル基のベンゼン環平面と C20 の距離に着目すると、B は A に比較してより近接している。これが、ジアステレオ選択性の向上 (**32a**, 64% de; **32d**, 78% de)に寄与していると考えられる。さらに C では、4-biphenyl 基が B よりも効果的に C20 を遮蔽しているために、ジアステレオ選択性が大幅に向上すると考えられる (**32k**, 84% de)。

以上の結果に基づき、著者は 4-biphenyl 体 **31k** をジアステレオ選択的エチル化の基質に用いて、実用的合成法を開発することとした。

2-4 T-2513 (5) の合成

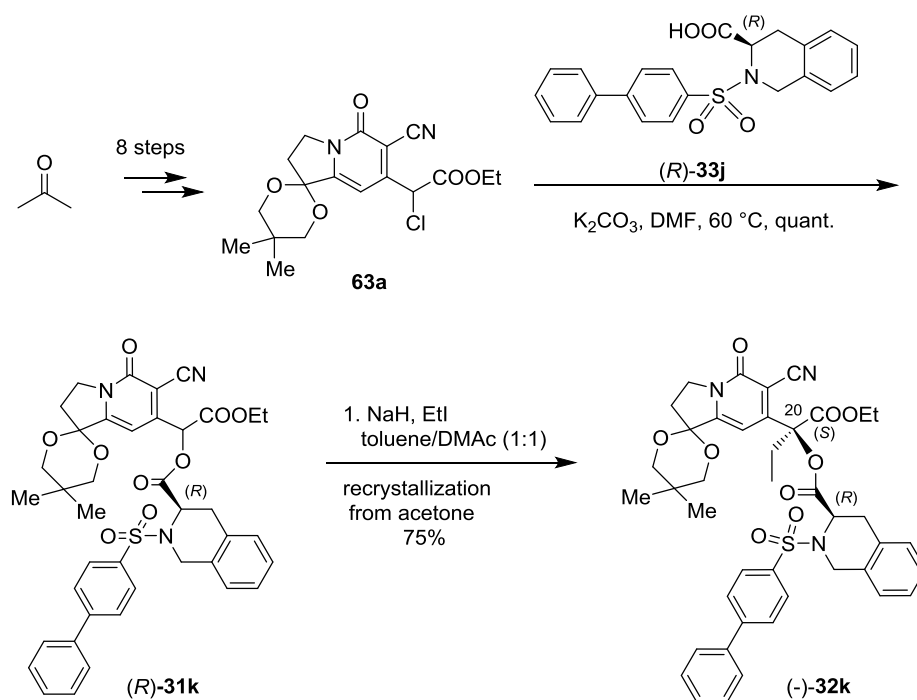
前項で見出した、高ジアステレオ選択的エチル化反応を鍵ステップに用いて、T-2513 (5)の全合成を検討した。

アセトンから 8 工程で合成したクロロエステル **63a**^[31]に対して DMF 中 K₂CO₃ 存在下に光学活性カルボン酸(*R*)-**33j**^[32]を反応させ、ジエステル(*R*)-**31k** を定量的な収率で得た。ジエステル(*R*)-**31k** を DMAc-トルエン(1:1 v/v)の混合溶媒中、NaH と iodoethane を用いてエチル化し、ジアステレオ選択性 87% de でエチル体(-)-**32k**へと誘導した。次いで、粗生成物をアセトンから再結晶し、化学的かつ光学的に純粋な(-)-**32k**を 75%収率で得ることに成功した(Scheme 2-3)。(-)-**32k**の C20 位絶対立体配置は、既知の三環性ケトン(*S*)-**14**へ誘導し、比旋光度を比較することにより*S*配置と決定した^[33]。

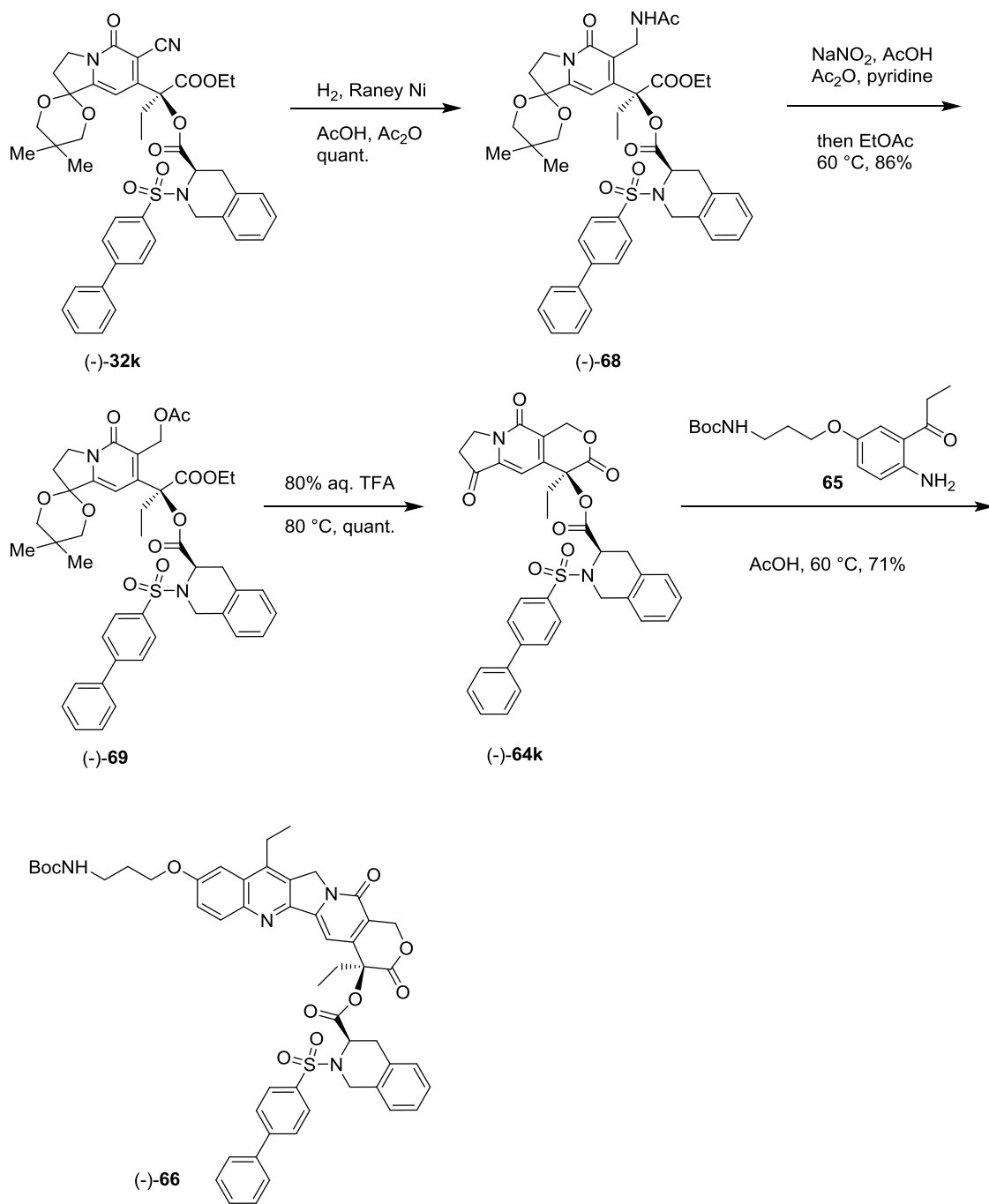
(-)-**32k**を AcOH-Ac₂O 溶媒中、常圧水素雰囲気下に Raney nickel 還元を行い、定量的な収率でアセトアミド(-)-**68**へと誘導した後、*N*-ニトロソ化と熱転位反応に付してアセテート(-)-**68**を 86%収率で得た。アセテート(-)-**68**を TFA-水(4:1 v/v)中で 80 °Cに加熱して、脱アセタール化とラクトン化を行い、三環性ケトン(-)-**64k**を定量的

な収率で得た。続いて、(-)-**64k** とアミノケトン **65**^[34]とを、AcOH 中 60 °Cにて Friedlander 縮合に供し、CPT 誘導体(-)-**66**とした (Scheme 2-4)。

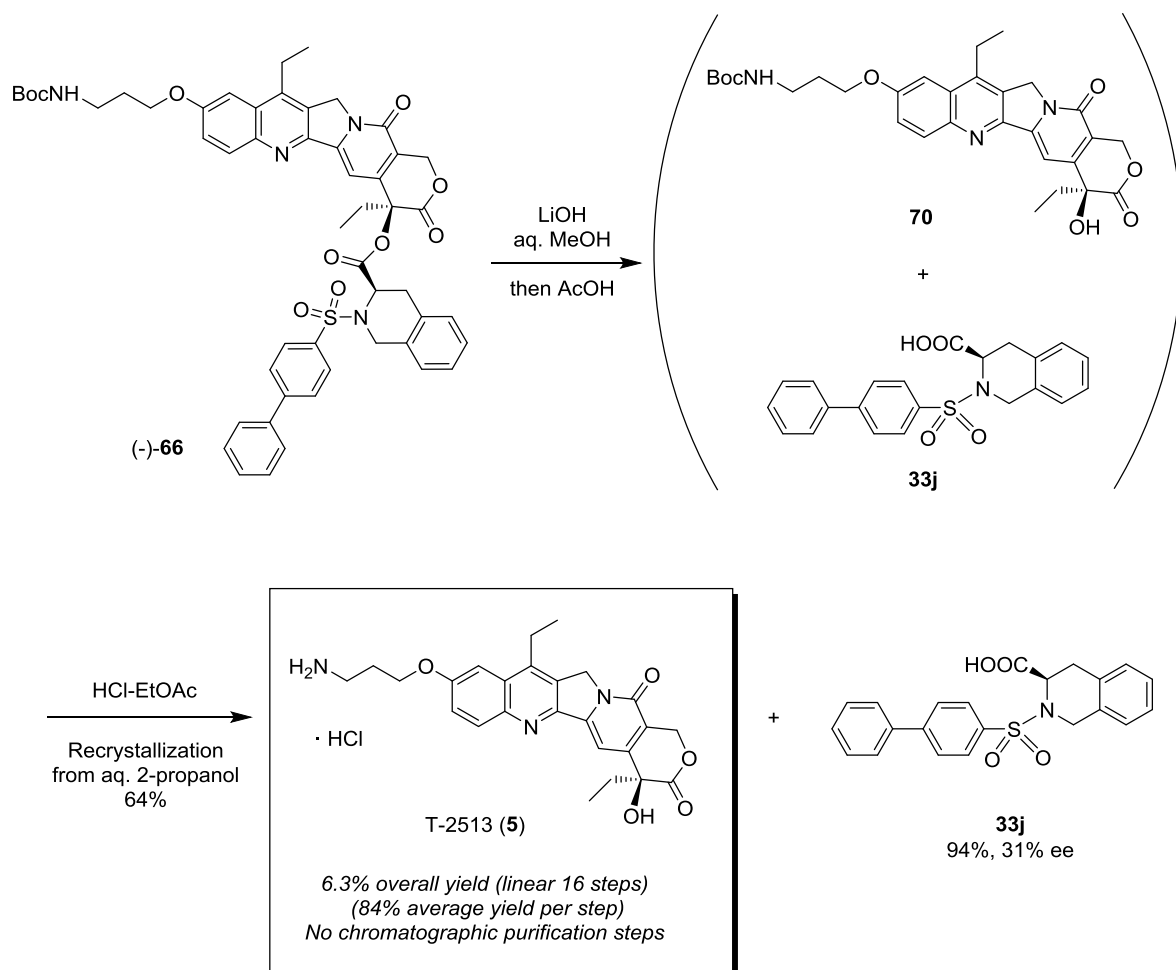
(-)-**66**を含水メタノール中 LiOH で処理することにより、不斉補助基のエステル部を加水分解した。この時、CPT 骨格のラクトン部も加水分解を受けたため、反応系中に AcOH を加えて酸性とし、再ラクトン化を行った。得られた **70** と **33j** の混合物を、HCl-EtOAc 中で攪拌すると、脱 Boc 化が進行して反応系中から T-2513 (**5**)が析出した。析出物を、ろ取することにより粗体の T-2513 (**5**)を得た。ろ液からは不斉補助基のカルボン酸 **33j** を 94%収率で単離することができたが、**33j** の光学純度は 31% ee に低下していた。最後に、粗体の T-2513 (**5**)を含水 2-propanol から再結晶すると、64% 収率 (from (-)-**66**) で高純度の T-2513 (**5**)を得ることができた (Scheme 2-5)。



Scheme 2-3. Synthesis of optically pure ethyl derivative (-)-**32k**.



Scheme 2-4. Synthesis of CPT derivative (-)-66.



Scheme 2-5. Synthesis of T-2513 (5).

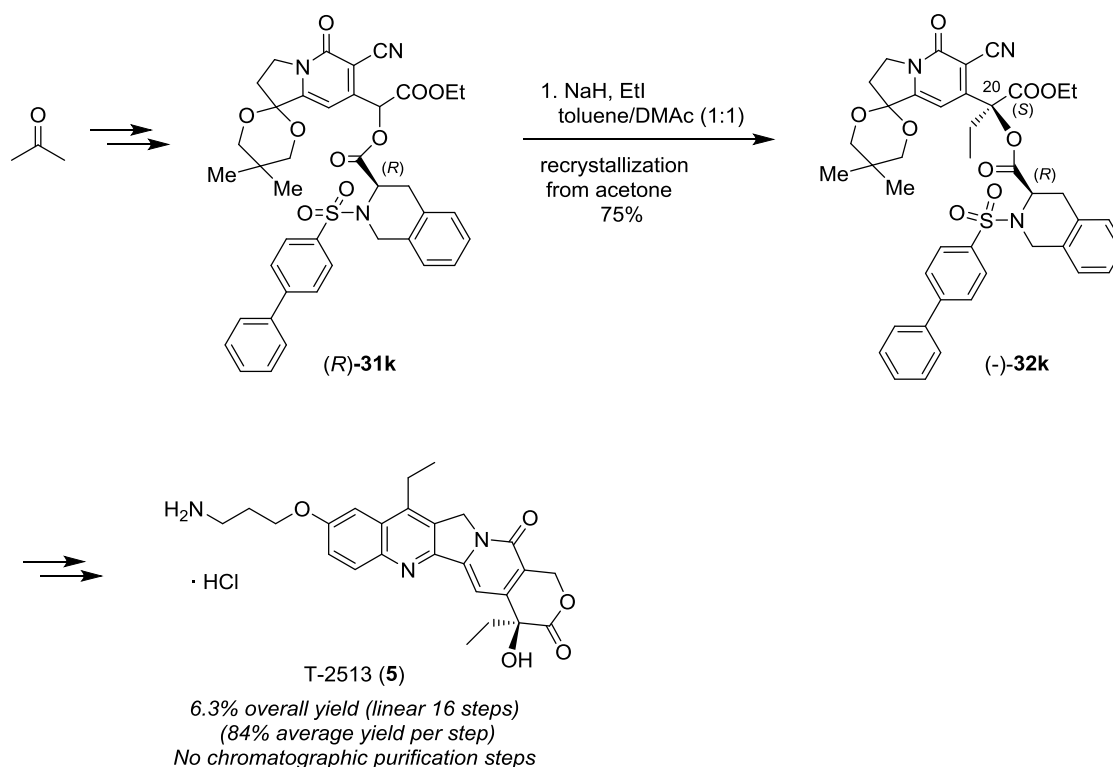
以上、アセトンから 16 工程、カラムクロマトグラフィー精製、OsO₄ 等の毒性の高い試薬、もしくは過酷な反応条件のいずれも使用することなく、総収率 6.3%(各工程平均収率 84%) で、グラムスケールの T-2513 (5) を取得可能な合成法を確立した。

2-5 結語

2 章において著者は、(R)-N-4-ビフェニルスルフォニル-1,2,3,4-テトラヒドロイソキノリンカルボン酸エステル (R)-31k のジアステレオ選択的エチル化、および再結晶により、光学的に高純度のエチル体(-)-32k を 75% 収率で得ることに成功した。本反応を鍵反応に用いて、水溶性 CPT 誘導体 T-2513 (5) のグラムスケールの合成法を確立することができた(アセトンから 16 工程、総収率 6.3%、各工程平均収率 84%)。本法は、当初設定した 3 つの必要条件、

- ◆ カラムクロマトグラフィー精製を必要としない。
- ◆ 毒性・危険性の高い試薬の使用が最小限に抑えられている。
- ◆ 極低温等の過酷な反応条件を必要としない。

を満たしており、大量合成に適用可能な実用性の高い合成法である^[35]。



Scheme 2-6. Summary of the synthesis of T-2513 (5).

第3章

グアニジン-ウレア触媒を用いたカンプトテシン合成鍵中間体の触媒的不斉合成

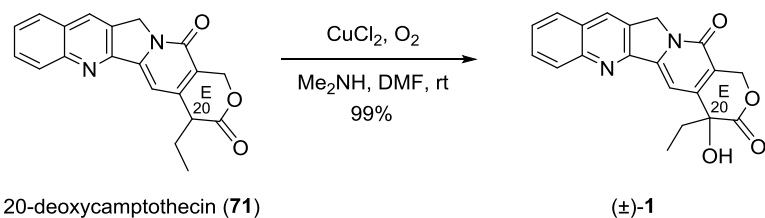
3-1 諸言

著者は第2章にて、水溶性 CPT 誘導体 T-2513 (5) の実用的合成法の開発に取り組み、鍵反応として高ジアステレオ選択的な C20 位不斉炭素の構築法を見出した。当方法は、カラムクロマトグラフィー精製、OsO₄ 等の毒性の高い試薬、もしくは過酷な反応条件のいずれも必要としない点を特長に持ち、大量合成に適用可能な実用性の高い合成法である。一方、当方法の弱点は、化学量論量の不斉補助基を必要とするため、合成工程数の増加や、製造コストの上昇に繋がっている点にある。著者は、この弱点を克服するべく、CPT の C20 位不斉炭素の触媒的不斉合成に取り組むこととした。

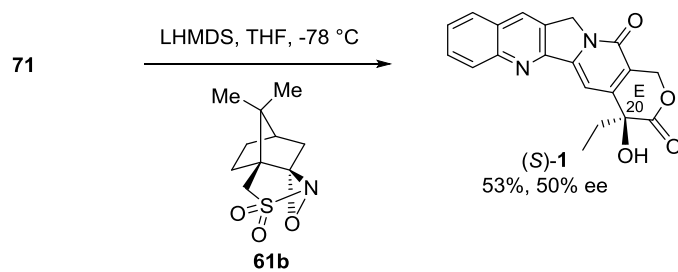
CPT の C20 位不斉炭素の触媒的不斉合成を目指し、著者が着目したアプローチは、E 部ラク톤の α -ヒドロキシ化である。その理由は、E 部ラク톤の触媒的不斉 α -ヒドロキシ化が、報告例のない新規アプローチであり、合成化学的にチャレンジングな点にある。E 部ラク톤の α -ヒドロキシ化は主に、1970~1980 年代のラセミ体 CPT の合成 (Scheme 3-1-a)^[36] に利用されてきた。2000 年代には Tagami (Scheme 3-1-b)^[37]、および Chen (Scheme 3-1-c)^[27] により E 部ラク톤の不斉 α -ヒドロキシ化が報告されたが、化学量論量のキラル酸化剤 **61**、および -78 °C の反応温度を必要とし、エナンチオ選択性はそれぞれ 50% ee、72% ee にとどまっている。

高収率かつ高エナンチオ選択的な E 部ラク톤の触媒的 α -ヒドロキシ化反応を開発することができれば、触媒的不斉ジオール化、もしくは触媒的不斉シアノシリル化に並ぶ、新しい範疇の CPT 合成法になると考えられる (Scheme 3-2)。

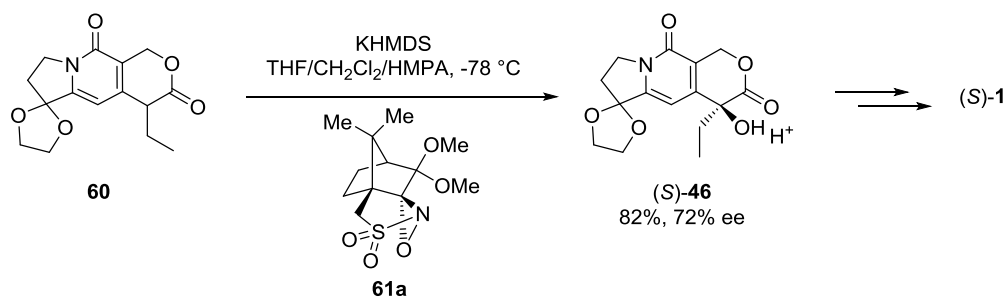
a) ラセミ体CPT(1)の合成



b) 化学量論量のキラルオキサジリジン61bを用いた(S)-1の不斉合成

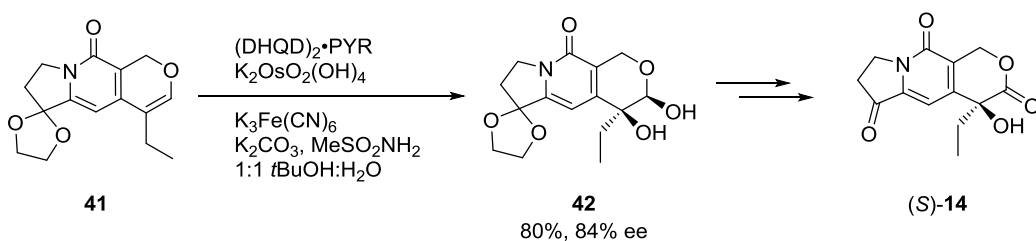
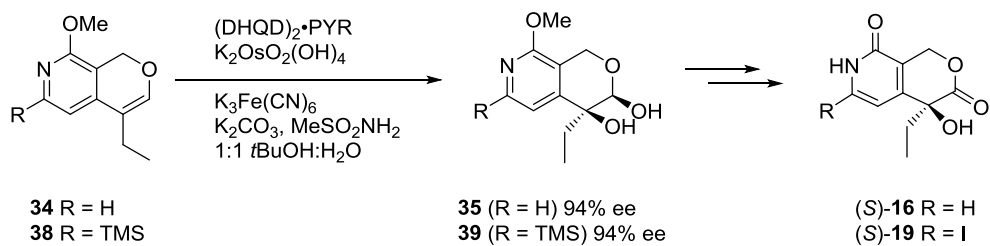


c) 化学量論量のキラルオキサジリジン61aを用いた(S)-1の不斉合成

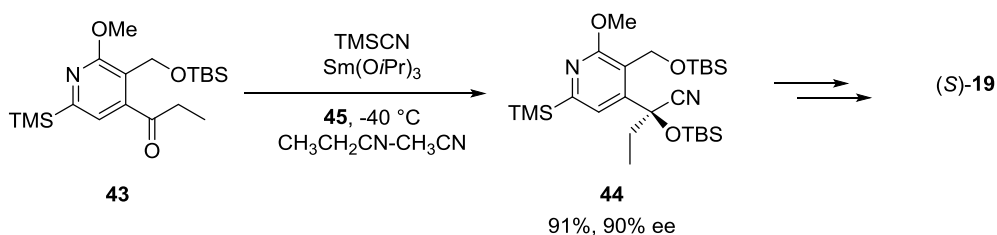


Scheme 3-1. α -Hydroxylation of 20-deoxycamptothecin (71) and lactone 60.

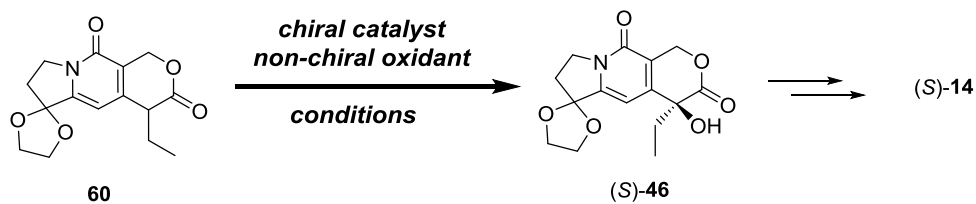
a) Catalytic asymmetric dihydroxylation approach



b) Catalytic asymmetric cyanosilylation approach



c) Catalytic asymmetric α -hydroxylation approach



Scheme 3-2. Catalytic reaction for construction of the stereogenic center at the C20 position of CPT.

著者の所属する長澤研究室では、グアニジン-チオウレア **72**、およびグアニジン-ウレア **62** が様々な立体選択的反応の優れた触媒になることを明らかにしてきた。これまでに、グアニジン部、キラルスペーサー部、および(チオ)ウレア部の広範な構造展開により、ニトロアルドール反応、ヘテロマイケル反応、もしくはエポキシ化に有効な触媒として **72a**^[40a]、**72b**^[40e]、**72c**^[40k]、ならびに **62a**^[40f]の開発に成功している (Figure 3-1)。

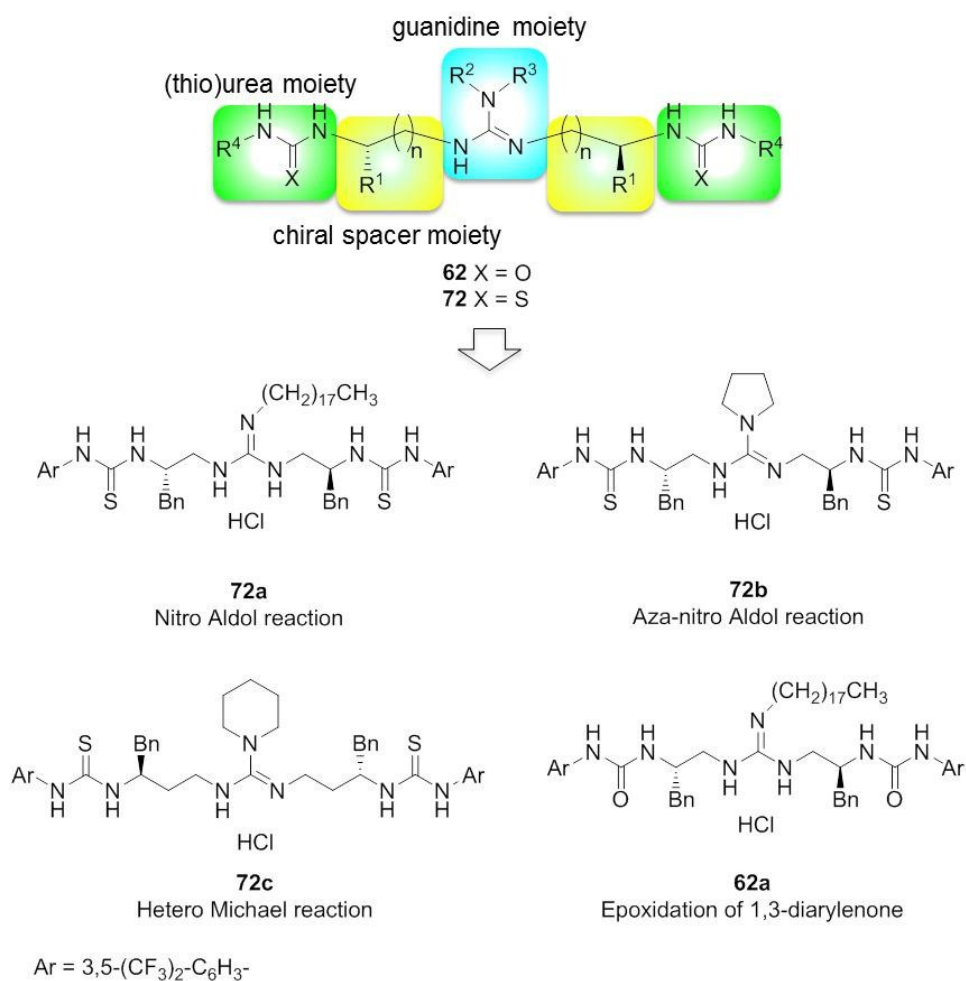
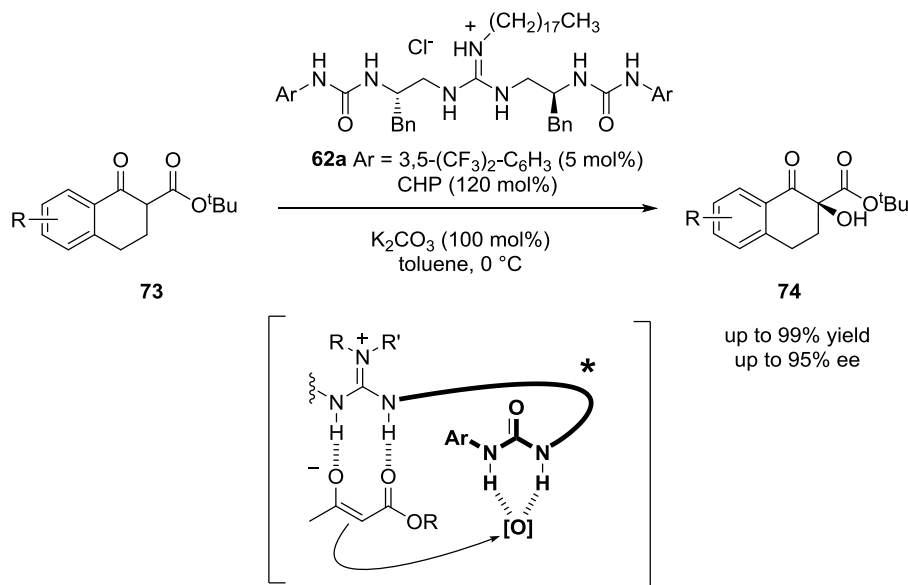


Figure 3-1. Guanidine-(thio)urea bifunctional organocatalysts in Nagasawa group.

最近著者らは、グアニジン-ウレア **62a** が、K₂CO₃、クメンペルオキシド (CHP)^[38]存在下に、β-ケトエステル **73** の不斉 α-ヒドロキシ化の触媒となることを見出した^[39]。本

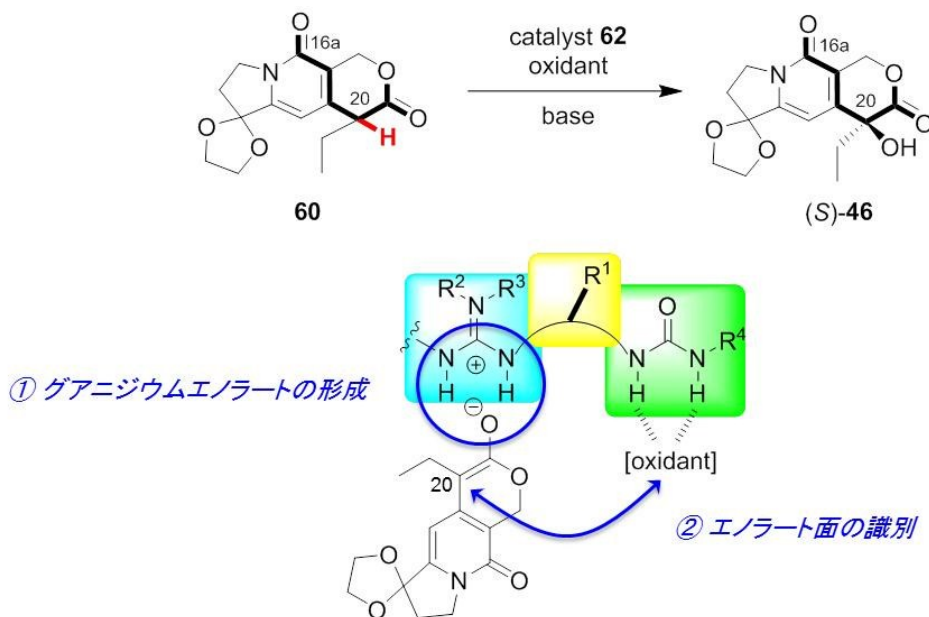
反応において **62a** のグアニジン部、ウレア部、および不斉炭素を有する鎖状部は、それぞれグアニジニウムエノラートの形成、酸化剤との水素結合形成、および不斉反応場の構築に寄与し、これらが協同的に作用して不斉 α -ヒドロキシ化反応を促進すると考えている^[40] (Scheme 3-3)。



Scheme 3-3. Asymmetric α -hydroxylation of β -ketoester **71** catalyzed by guanidine-urea bifunctional organocatalyst **62a**, and a plausible interacting model of the reaction.

著者らが見出した触媒的不斉 α -ヒドロキシ化反応は、ラクトン **60** へ適用できる可能性がある。グアニジン-ウレア **62** を触媒に用いて、ラクトン **60** から高エナンチオ選択的に (*S*)-**46** を取得するためには、Scheme 3-3 の相互作用モデルに基づき、以下の2点を満たすことが必要と考えられる。すなわち、①反応条件下にラクトン **60** からグアニジニウムエノラートを発生させる、および②触媒によって形成される不斉反応場にエノラートを固定し、酸化剤をエノラートの *Si*-面選択的に接近させることが鍵となる (Scheme 3-4)。①については、K₂CO₃ 程度の強さの塩基であっても **60** のエノラートが生成する可能性がある。**60** の C20 位水素は、ラクトンの α 位、かつ C16a 位カルボニル基のビニログス位を占めており、通常のラクトン α 位水素より高い酸性度を持つと

予想される。したがって、強塩基を用いなくとも、**60** のエノラートが生成し、触媒のグアニジン部と相互作用する可能性がある。また、②については、グアニジン-ウレア **62** のキラルスペーサー部、グアニジン部、もしくはウレア部を変換することにより、**60** に最適な構造を見出すことができると考えられる。



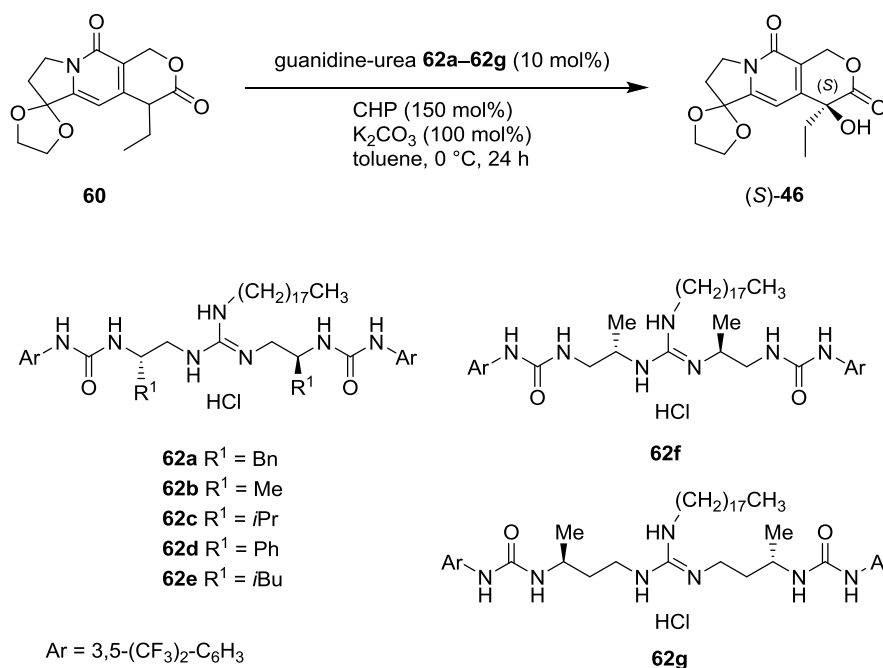
Scheme 3-4. Asymmetric α -hydroxylation of lactone with vinyllogous pyridone **60** using guanidine-urea bifunctional organocatalyst **62**.

3-2 グアニジン-ウレア触媒を用いた触媒的不斉 α -ヒドロキシ化の開発

初期検討として、ラクトン **60**^[41]に対して β -ケトエステル **71** の α -ヒドロキシ化に用いた反応条件を適用した。すなわち、**60** をトルエン中、塩基として K_2CO_3 、酸化剤としてクメンペルオキシド (CHP)、触媒としてグアニジン-ウレア **62a**^[40f]を用いて 0 °C にて反応を行った。その結果、目的の α -ヒドロキシ体 (*S*)-**46** を 99%収率、22% ee で得ることができた (Table 3-1, entry 1)。一方、**62a** を添加しない場合には、 α -ヒドロキシ化は進行しなかった (Table 3-1, entry 2)。これらの結果から、グアニジン-ウレア **62a** は、反応の進行に必須な触媒として機能していることがわかった。また、低いながらも 22% ee のエナンチオ選択性が発現したことから、**62a** により必要な不斉反応場が構築されていることを確認することができた。

そこで、エナンチオ選択性の向上を目的に、グアニジン-ウレア触媒 **62**^[42]の各部構造変換を行うこととした (Table 3-1, entries 3–8)。まず初めに、キラルスペーサー部の置換基 R^1 を変換し、反応のエナンチオ選択性を評価した。触媒 **62b**^[40f] ($R^1 = Me$)、および **62c**^[40f] ($R^1 = iPr$) の場合、触媒 **62a** を用いた時に比較して選択性はそれぞれ 52%、および 49% ee へと向上した (entries 3 and 4)。一方、**62d** ($R^1 = Ph$)、もしくは嵩高い置換基を有する **62e** ($R^1 = iBu$) では、選択性の向上は認められなかった (entries 5 and 6)。これらの結果から、ラクトン **60** を基質に用いる場合、置換基 R^1 は立体障害の小さい方がエナンチオ選択性向上に寄与することがわかった。続いて、グアニジン部に近接する炭素上にメチル基を置換した **62f** を用いた場合、**62b** の場合に比較して著しく選択性が低下することがわかった (entry 7 vs. entry 3)。また、スペーサー部のメチレン鎖を1炭素伸長した **62g** の場合も、著しく選択性が低下することがわかった (entry 8)。

Table 3-1. Asymmetric α -hydroxylation of lactone **60** using guanidine-urea bifunctional organocatalysts **62a–62h**.^[a]

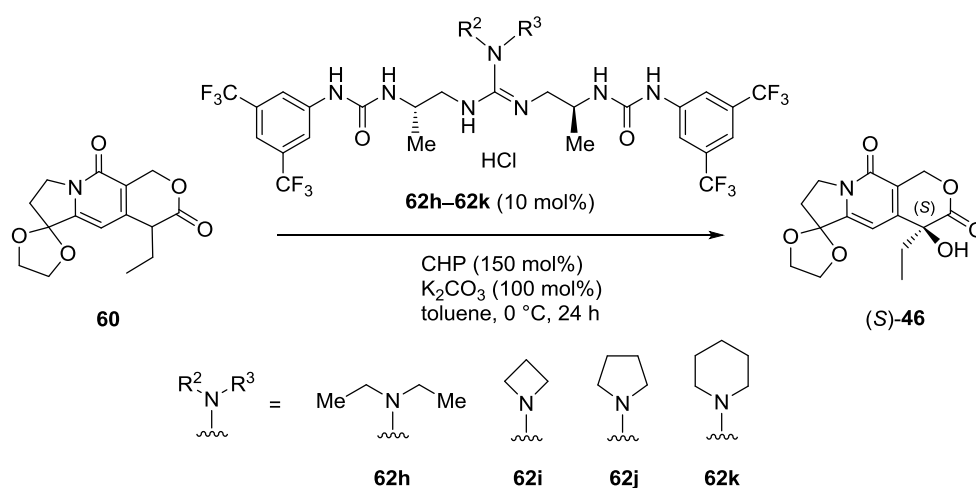


entry	catalyst	(S)-46	
		Yield (%)	ee (%) ^[b]
1	62a	99	22
2	無し	0	—
3	62b	70	52
4	62c	89	49
5	62d	93	20
6	62e	97	37
7	62f	95	10
8	62g	82	11

[a] Reactions were performed with **60** (0.1 mmol), CHP (0.15 mmol), K₂CO₃ (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] Racemic **46** and (S)-**46** were prepared according to references 19b and 35, respectively. The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC.

次に、グアニジン部置換基 R^2 、 R^3 について検討を行った (Table 3-2)。オクタデシルアミノ基 **62b** をジエチルアミノ基 **62h**、もしくはアゼチジノ基 **62i** へと変換すると、エナンチオ選択性はそれぞれ 65%、および 66% ee へと向上した (entries 1 and 2)。さらに、ピロリジン置換体 **62j** へと変換した場合には、76% ee のエナンチオ選択性で (*S*)-**46** を得ることができた (entry 3)。しかし、ピペリジン置換体 **62k** では、選択性は 56% ee にとどまった (entry 4)。

Table 3-2. Asymmetric α -hydroxylation of lactone **60** using guanidine-urea bifunctional organocatalysts **62h–62k**.^[a]

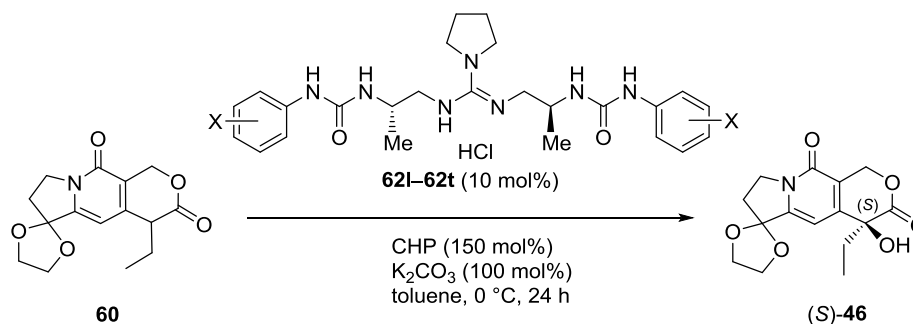


entry	catalyst	<i>(S)</i> - 46	
		Yield (%)	ee (%) ^[b]
1	62h	94	65
2	62i	99	66
3	62j	97	76
4	62k	92	56

[a] Reactions were performed with **60** (0.1 mmol), CHP (0.15 mmol), K_2CO_3 (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] Racemic **46** and (*S*)-**46** were prepared according to references 19b and 35, respectively. The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC.

続いて、ウレア部のベンゼン環上置換基がエナンチオ選択性に及ぼす影響を評価することとした (Table 3-3)。無置換ベンゼン **62l** を用いた場合には、選択性が 70% ee へと低下した (entry 1)。一方、3,5-di-F 体 **62m** では、**62j** と同程度の選択性を示した (entry 2)。また、2-CF₃ 体 **62n**、もしくは 3-CF₃ 体 **62o** が、**62j** と同程度の選択性を示したことから (entries 3 and 4)、ベンゼン環の 3,5-di-置換は選択性の発現に必須ではないことがわかった。興味深いことに、4-CF₃ 体 **62p** を用いた場合、選択性が向上し、95%収率、84% ee で (*S*)-**46** を得ることができた (entry 5)。そこで、4 位置置換体をさらに検討することにした。4-F 体 **62q**、4-OCF₃ 体 **62r**、および 4-NO₂ 体 **62s** は、**62p** と同程度の選択性を示した (entries 6-8)。しかし、4-OMe 体 **62t** では選択性が低下することがわかった (entry 9)。これまでの検討で最も高い選択性を示した **62p** の使用量を 5 mol% に減量して反応を行ったところ、化学収率、エナンチオ選択性ともに低下しないことがわかった (entry 10)。さらに、(*S*)-**46** の光学純度は、エタノールからの再結晶により 93% ee に向上することがわかった (entry 10)。

Table 3-3. Asymmetric α -hydroxylation of lactone **60** using guanidine-urea bifunctional organocatalysts **62l–62t**.^[a]



entry	catalyst		5a	
	X	Yield (%)	ee (%) ^[b]	
1	62l	H	93	70
2	62m	3,5-di-F	86	76
3	62n	2-CF ₃	89	75
4	62o	3-CF ₃	93	78
5	62p	4-CF ₃	95	84
6	62q	4-F	99	82
7	62r	4-OCF ₃	85	83
8	62s	4-NO ₂	96	82
9	62t	4-OMe	70	78
10	62p ^[c]	4-CF ₃	93	84, 93 ^[d]

[a] Reactions were performed with **60** (0.1 mmol), CHP (0.15 mmol), K₂CO₃ (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] Racemic **46** and (*S*)-**46** were prepared according to references 19b and 35, respectively. The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC. [c] Reaction was carried out with 5 mol% of catalyst **62p**. [d] Enantiomeric purity was increased into 93% ee by a single recrystallization from ethanol.

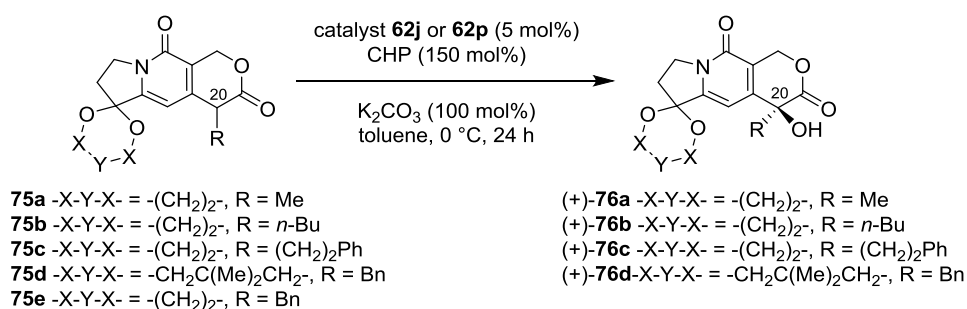
以上のように、グアニジン-ウレア **62p** を触媒に用いた不斉 α -ヒドロキシ化により、合成鍵中間体 (*S*)-**46** を高収率 (95%)、かつ高エナンチオ選択的 (84% ee) に得るこ

とに成功した。

3-3 触媒的不斉 α -ヒドロキシ化の適用範囲拡大

次に、本反応の適応範囲を確認するため、C20 位に種々のアルキル基を置換した **75**^[43] の触媒的不斉 α -ヒドロキシ化を検討した (Table 3-3)。

Table 3-4. Asymmetric α -hydroxylation of lactones **75a–75d** using guanidine-urea bifunctional organocatalyst **62j** or **62p**.^[a]



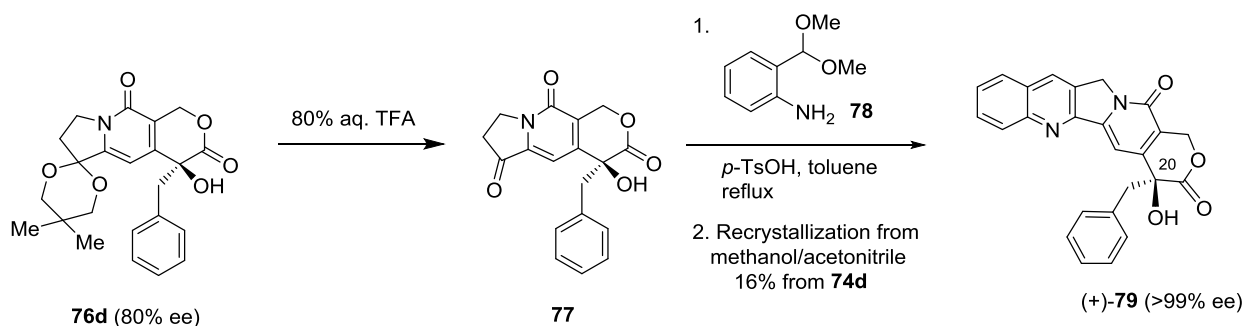
entry	substrate	catalyst	Product ^[b]	
			yield (%)	ee (%) ^[c] [d]
1	75a	62j	(+)- 76a	99, 75
2	75b	62p	(+)- 76b	95, 82
3	75c	62p	(+)- 76c	90, 82
4	75d ^[e]	62j	(+)- 76d	99, 80, 90 ^[f]

[a] Reactions were performed with **75** (0.1 mmol), CHP (0.15 mmol), K₂CO₃ (0.1 mmol), and catalyst (0.005 mmol) in toluene at 0 °C for 24 h. [b] Racemic α -hydroxy lactones **76a–76d** for HPLC analysis were derived from lactones **75a–75d** by reaction with NaHMDS and (\pm)-*N*-tosyl-phenyloxaziridine^[44] in THF. [c] The enantiomeric excess was determined by chiral HPLC. [d] Absolute stereochemistries were deduced from the results of oxidation of **60**. [e] Oxidation did not proceed in the case of **75e** with ethylene dioxide-derived acetal at C2 because of its insolubility. Thus, we examined the reaction with **75d** bearing neopentyl glycol-derived acetal. [f] Enantiomeric purity was increased into 90% ee by a single recrystallization from ethanol.

C20 位 Me 体 **75a**、*n*Bu 体 **75b**、および 1-phenylethyl 体 **75c** は、いずれの場合も

高収率、かつ良好なエナンチオ選択性でヒドロキシ体を与えた (entries 1-3)。C20位 Bn 体については、エチレンアセタール体 **75e** がトルエンに難溶で反応が進行しなかったため、ネオペンチルグリコールアセタール体 **75d** を基質に用いて反応を行った。その結果 99%収率、80% ee でヒドロキシ体(+)-**76d** を得ることができた (Table 3-3, entry 4)。さらに、(+)-**76d** (80% ee)をエタノールから再結晶することにより、光学純度を 90% ee に向上させることができた (entry 4)。

続いて、(+)-**76d** (80% ee)を用いて、C20-desethylbenzyl camptothecin (**79**)^[45]の合成を行うことにした (Scheme 3-3)。(+)-**76d** (80% ee)を 80% TFA を用いて脱アセタール化し、三環性ケトン **77** を得た。三環性ケトン **77** と、別途調製したアニリン **78**^[46]とをトルエン中 *p*-TsOH 存在下に加熱することにより Friedlander 縮合を行い、(+)-**79** を合成した。粗体の(+)-**79**をメタノール/アセトニトリルから再結晶することにより、16%収率、>99% ee で化学的かつ光学的に高純度の(+)-**79** を得ることができた。

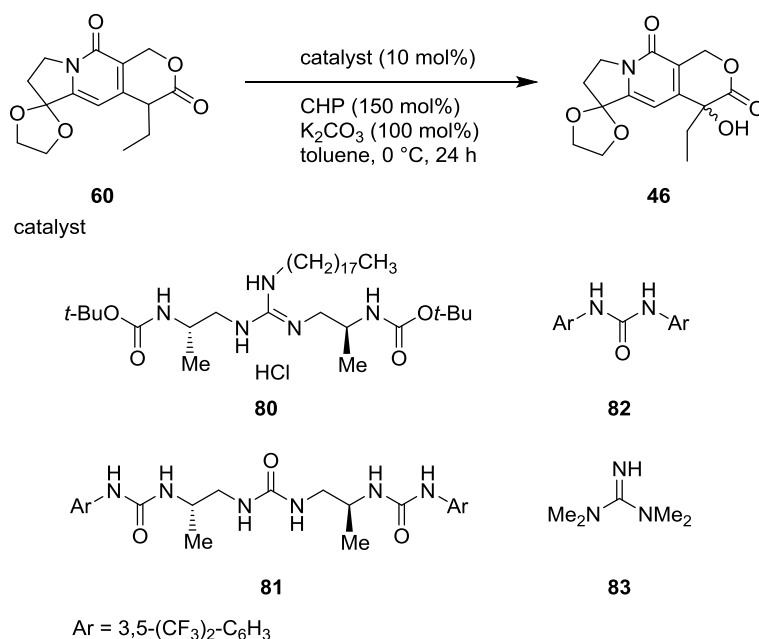


Scheme 3-5. Synthesis of (+)-C20-desethylbenzyl camptothecin (**79**).

3-4 触媒作用発現に必要な部分構造の解明

グアニジン-ウレア **62** の、グアニジン、およびウレアの各部の必要性を考察するため、各部が欠失した誘導体 **80-81**^[47]を用いて、Table 3-2, entry 5 の反応条件下にラクトン **60** の α -ヒドロキシ化を検討した (Table 3-5)。

Table 3-5. Cooperative effects of guanidine and urea and the chiral spacer in α -hydroxylation catalysts.^[a]



entry	catalyst	additive (eq.)	46		
			yield (%)	ee (%)	<i>R</i> or <i>S</i> ^[b]
1	62b	—	70	52	<i>S</i>
2	80	—	trace	—	—
3	80	82 (0.1 eq.)	85	8	<i>R</i>
4	81	—	25	7	<i>S</i>
5	81	83 (0.1 eq.)	64	5	<i>S</i>

[a] Reactions were performed with **60** (0.1 mmol), CHP (0.15 mmol), K₂CO₃ (0.1 mmol), and catalyst (0.01 mmol) in toluene at 0 °C for 24 h. [b] The enantiomeric excess and the absolute stereochemistry were determined by chiral HPLC. [c] Racemic **46** and (*S*)-**46** were prepared according to references 21b and 36, respectively.

グアニジン**80** (ウレア部欠失) もしくは、トリウレア**81** (グアニジン部欠失) を単独で用いた場合、 α -ヒドロキシ化は極めて低収率でしか進行せず、エナンチオ選択性はほとんど発現しなかった (entries 2 and 4)。一方、反応系中にウレア**82**^[48]、もしくは、グアニジン**83** を添加すると、 α -ヒドロキシ化が促進され、各 85%、および 64% 収率で

46 を得ることができた。しかし、エナンチオ選択性の改善は認められなかった (entries 3 and 5)。以上の結果から、60 の不斉 α -ヒドロキシ化を効果的に進行させるために、グアニジンとウレアの両方の官能基が必須であること、さらに、高いエナンチオ選択性の発現には、グアニジンとウレアが同一分子内に共存することが重要であることがわかった。

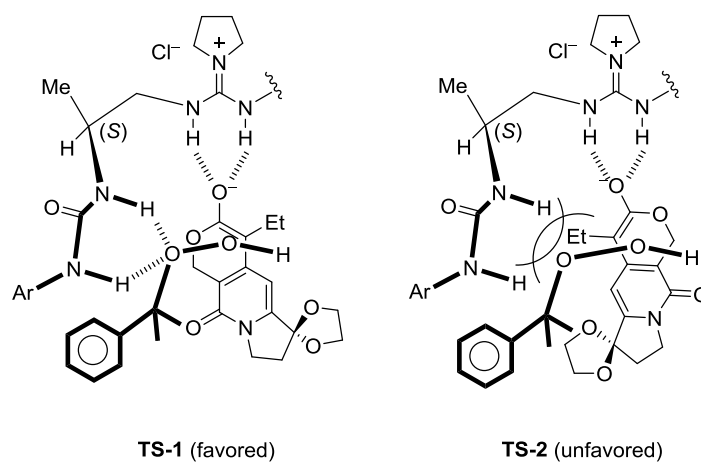
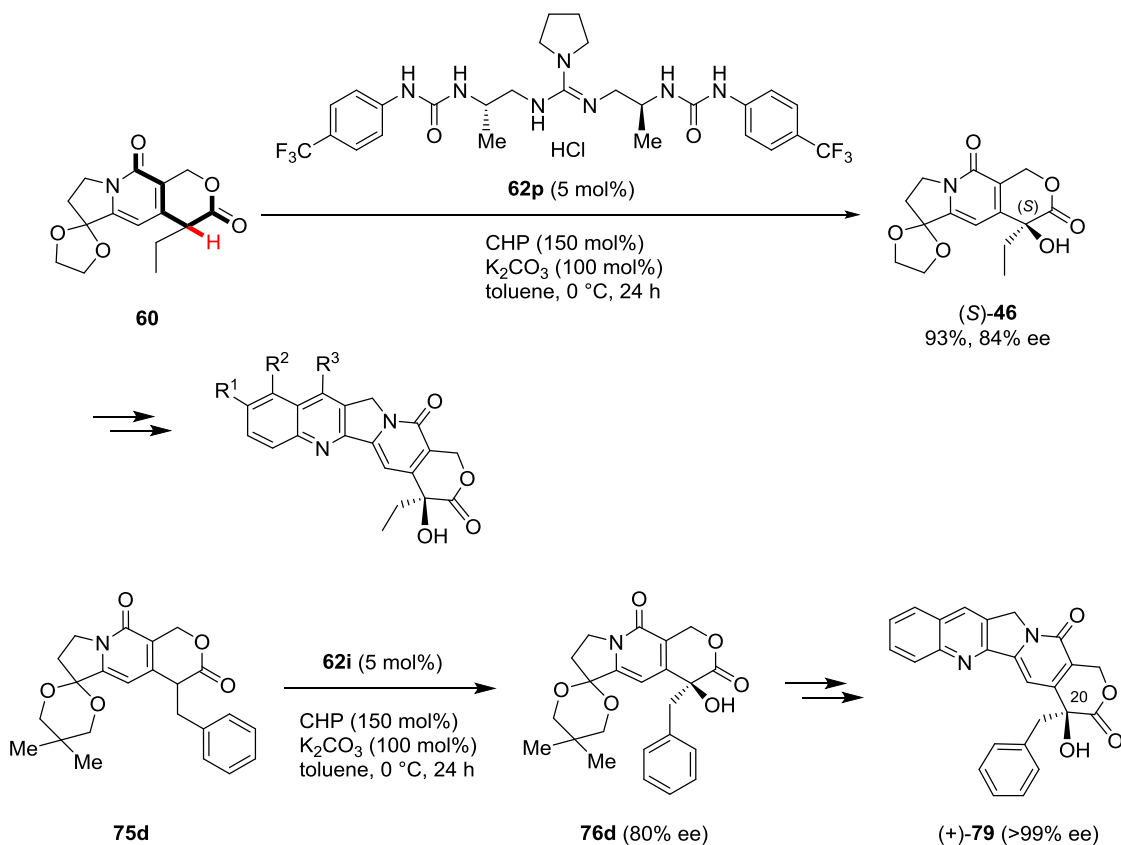


Figure 3-2. Plausible transition state of the α -hydroxylation catalyzed by 62.

ラクトン 60 のヒドロキシ化のエナンチオ選択性が(S)-選択的である点を踏まえ、本反応の推定遷移状態を提示した (Figure 3-2)。触媒のグアニジン部と、ラクトン 60 から生じるエノレートとのイオン対形成、および、ウレア部と CHP との水素結合形成を考慮すると、遷移状態として TS-1 もしくは TS-2 が想定される。両者を比較すると、60 のエチル基とウレア部との立体反発がより少ない TS-1 を経由した反応が優先的に進行し、(S)-46 を与えると考えられる。

3-5 結語

3章において著者は、グアニジン-ウレア **62p** を用いた、ビニロガス型ラクトン **60** の触媒的不斉ヒドロキシ化を開発し、CPT、および CPT 誘導体の鍵合成中間体 (*S*)-**46** の高エナンチオ選択的合成に成功した。また、グアニジン-ウレア **62** の構造-触媒活性相関を検討し、グアニジン、およびウレアの両方が反応促進に必須であること、および、両者が同一分子内に共存することが高いエナンチオ選択性の発現に重要であることを明らかとした。さらに、本章で開発した新規触媒的不斉 α -ヒドロキシ化の応用例として、C20 位置換 CPT 誘導体(+)-**79** の不斉合成を達成した^[49]。



Scheme 3-6. Summary of Chapter 3.

第4章

結論

本研究において著者は、抗腫瘍薬として有用な CPT 誘導体の効率的な不斉合成法の開発を目指し、鍵ステップである C20 位不斉炭素の構築に取り組んだ。その結果、ジアステレオ選択的エチル化、および触媒的不斉ヒドロキシ化の2種類の合成法を見出すことに成功した。

第2章では、(*R*)-*N*-4-ビフェニルスルフォニル-1,2,3,4-テトラヒドロイソキノリンカルボン酸 ((*R*)-**33j**)を不斉補助基に用いた、高ジアステレオ選択的な CPT C20 位不斉炭素の構築法を開発し、光学的に純粋な中間体(-)-**32k**を75%収率で得ることに成功した。本反応を鍵反応に用いて、水溶性 CPT 誘導体 T-2513 (**5**)の合成法を確立することができた。出発原料のアセトンから16工程、総収率6.3%で T-2513 (**5**)を合成する本合成法は、①カラムクロマトグラフィー精製を必要としない、②毒性・危険性の高い試薬の使用が最小限に抑えられている、③極低温等の過酷な反応条件を必要としない点で、大量合成に適用できる実用性の高い合成法である。

第3章では、グアニジン-ウレア **62p**を用いた、ビニログス型ラクトン **60**の触媒的不斉ヒドロキシ化を開発し、CPT、および CPT 誘導体の鍵合成中間体 (*S*)-**46**の高エナンチオ選択的合成に成功した。また、**62**の構造-触媒活性相関を検討し、グアニジン、およびウレアの両方が反応促進に必須であること、および、両者が同一分子内に共存することが高いエナンチオ選択性の発現に重要であることを明らかにした。さらに、本章で開発した新規触媒的不斉ヒドロキシ化の応用例として、C20 位置換 CPT 誘導体(+)-**79**の不斉合成を達成した。本反応は、①安価で大量に購入できるクメンペルオキシド (CHP)を酸化剤に用いる、②極低温等の過酷な反応条件を必要としない、③重金属試薬を使用しないといった実用性の高い特長を有している。

以上、本研究において著者は、実用性の高いCPT誘導体C20位構築法の開発に成功した。これらの方法は、CPT 誘導体のみならず、天然物や医薬品候補化合物の合成に活用できる可能性を有しており、今後、有用性の拡大が期待される。

実験の部

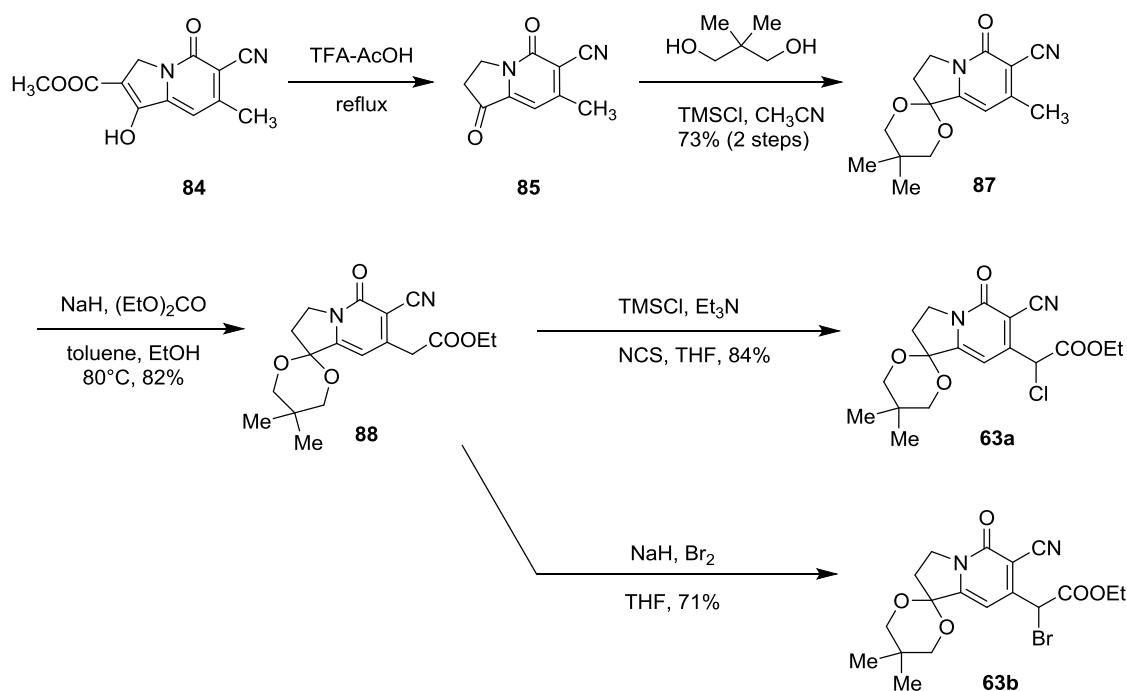
General Remarks

Flash chromatography was performed using silica gel 60 (spherical, particle size 0.040–0.100 mm, Kanto Co., Inc., Japan) or NH silica gel (spherical, particle size 0.06 mm, Fuji Silysia Chemical LTD., Japan). Optical rotations were measured on a JACO P-2200 polarimeter. ^1H and ^{13}C NMR spectra were recorded on AL300 (JEOL), ECX400 (JEOL), JNM500 (JEOL), or AVANCE400 (Bruker) instruments. Chemical shifts in chloroform-*d*, methanol-*d*₄, or dimethylsulfoxide-*d*₆ were reported in the scale relative to chloroform-*d* (7.26 ppm), methanol-*d*₄ (3.30 ppm) and dimethylsulfoxide-*d*₆ (2.50 ppm) for ^1H NMR, respectively. For ^{13}C NMR, chemical shifts were reported in the scale relative to chloroform-*d* (77.0 ppm), methanol-*d*₄ (49.0 ppm), or dimethylsulfoxide-*d*₆ (39.5 ppm) as internal references, respectively. Mass spectra were recorded on JMS-T100LC (JEOL) spectrometer. Melting points were measured on a Büchi model B-545 instrument without correction. Elemental analyses were performed using a Perkin-Elmer 2400 CHN-Analyzer and Yokogawa IC7000S ion chromatograph (oxygen flask method).

第2章の実験

Synthesis of compounds 31b–31o

Synthesis of α -halo esters 63a and 63b



Scheme S1. Synthesis of α -halo esters **63a** and **63b**.

Tetrahydroindolizine **87**: A suspension of **84**^[15] (50.6 g, 0.21 mol) in AcOH (400 mL) and TFA (80 mL) was heated to reflux for 7.5 hours, and then concentrated to 1/3 volume under reduced pressure. To the residue was added *i*-Pr₂O (720 mL). The resulting precipitate was collected by filtration and washed with *i*-Pr₂O (200 mL) to give 39.2 g of **85** as a dark purple solid. To a suspension of **85** (39.2 g) and 2,2-dimethyl-1,3-propanediol (64.6 g, 0.62 mol) in CH₃CN (400 mL) was added TMSCl (45.1 g, 0.42 mol) dropwise over 10 minutes at 15 °C. The mixture was stirred for 4 hours at room temperature, and then poured into 0.4 mol/L aqueous NaHCO₃ solution (1.5 L). The resulting precipitate was collected by filtration, washed with water (500 mL), and then air-dried. The obtained solid was recrystallized from CHCl₃/EtOH to give 41.4 g (73%, 2 steps) of **87** as dark green crystals: mp 225–229 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.87 (s, 3H), 1.30 (s, 3H), 2.49 (s, 3H), 2.51–2.57 (m, 2H), 3.63 (br d, *J* = 12 Hz, 2H), 3.69 (br d, *J* = 12 Hz, 2H),

4.15 (t like, $J = 6.7$ Hz, 2H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.5, 22.0, 22.6, 28.8, 30.5, 46.1, 72.6, 102.7, 104.1, 105.4, 115.0, 152.3, 158.7, 160.9; IR (Nujol) 2222, 1647 cm^{-1} ; MS (APCI) m/z 275 ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: C 65.68, H 6.61, N 10.21; found: C 65.42, H 6.53, N 10.10.

Ester **88**: A suspension of **87** (54.6 g, 0.20 mol) and NaH (60% oil suspension, 35.0 g, 0.88 mol) in toluene (1.1 L) was gradually heated to 80 °C under an argon atmosphere. The mixture was stirred at 80 °C for 1 hour, and then a mixture of diethyl carbonate (94.0 g, 0.80 mol) and EtOH (3.67 g, 0.08 mol) was added dropwise to it over 10 minutes. The whole mixture was stirred at 80 °C for 2 hours, and then cooled to 5 °C. To it were added 50% aqueous AcOH (300 mL) dropwise, CHCl_3 (1.2 L), and water (500 mL). The organic phase was separated, and the aqueous phase was extracted with CHCl_3 (500 mL). The combined organic phases were washed with water (2×1 L) and saturated aqueous NaCl solution. The organic phase was dried over MgSO_4 , treated with activated charcoal, filtered through Celite, and then evaporated under reduced pressure. To a solution of the residual solid in EtOAc (1 L) and CHCl_3 (1 L) was added silica gel (250 g), and the mixture was stirred for 30 minutes. The silica gel was filtered off, washed with 1:1 EtOAc/ CHCl_3 (2×1 L), and the filtrate and washings were evaporated under reduced pressure. The residual green solid was recrystallized from EtOAc/*i*-Pr₂O. Crystals were collected by filtration, washed with *i*-Pr₂O, and then dried under reduced pressure at 50 °C to give 56.7 g (82%) of **88** as pale green prisms: mp 150–151 °C; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (s, 3H), 1.28 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 2.51–2.57 (m, 2H), 3.63 (br d, $J = 11$ Hz, 2H), 3.65 (br d, $J = 11$ Hz, 2H), 3.79 (s, 2H), 4.13–4.18 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 22.0, 22.6, 29.0, 30.4, 40.3, 46.3, 61.8, 72.5, 102.4, 105.2, 105.4, 114.5, 152.9, 155.7, 158.5, 167.8; IR (Nujol) 2220, 1725, 1652 cm^{-1} ; MS (APCI) m/z 347 ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$: C 62.42, H 6.40, N 8.09; found: C 62.19, H 6.26, N 7.91.

α -Chloro ester **63a**: To a suspension of **88** (43.4 g, 0.125 mol) in THF (600 mL) was added Et_3N (13.9 g, 0.138 mol) at 4 °C under an argon atmosphere. To the suspension was added TMSCl (14.4 g, 0.133 mmol) dropwise over 5 minutes at –4 °C. The mixture was stirred for 1 hour at the same temperature, then a suspension of *N*-chlorosuccinimide (17.0 g, 0.127 mol) in THF (400 mL) was added dropwise to it over 7 minutes keeping the temperature below 4 °C. Stirring was continued for 4.5 hours at 0–4 °C, to the reaction mixture was added water (1 L) at 0 °C, and then the

mixture was extracted with EtOAc (2×1 L). The combined organic extracts were washed with water (2×800 mL) and saturated aqueous NaCl solution (800 mL), dried over Na_2SO_4 , treated with activated charcoal (15 g), filtered through Celite, and then evaporated under reduced pressure. The resulting pale yellow crystals were recrystallized from EtOAc/*i*-Pr₂O to give 40.3 g (84%) of **63a** as colorless needles: mp 153–155 °C; ¹H NMR (400 MHz, CDCl₃): δ 0.88 (s, 3H), 1.28 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 2.52–2.58 (m, 2H), 3.60–3.70 (m, 4H), 4.13–4.21 (m, 2H), 4.22–4.37 (m, 2H), 5.63 (s, 1H), 6.77 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 22.1, 22.7, 22.8, 29.2, 30.5, 46.5, 55.5, 63.7, 72.5, 99.7, 104.1, 105.3, 113.6, 154.2, 156.0, 157.9, 165.5; IR (Nujol) 2227, 1749, 1662 cm⁻¹; MS (APCI) m/z 381 ([M+H]⁺); elemental analysis calcd (%) for C₁₈H₂₁ClN₂O₅: C 56.77, H 5.56, N 7.36, Cl 9.31; found: C 56.69, H 5.63, N 7.17, Cl 9.01.

α -Bromo ester **63b**: To a suspension of **88** (67.94 g, 0.196 mol) in THF (1.1 L) was added NaH (60% oil suspension, 9.41 g, 0.235 mol) at room temperature under an argon atmosphere, and then the mixture was stirred for 1 hour. To the mixture was added Br₂ (40.28 g, 0.252 mol) in one portion at 3 °C. The mixture was stirred at room temperature for 1 hour, and then cooled in an ice bath. To the mixture were cautiously added an aqueous citric acid solution (300 mL) and 10% aqueous Na₂S₂O₃ solution (300 mL). The mixture was diluted with water, and then extracted with CHCl₃ (500 + 700 mL). The combined organic extracts were washed with water (3×1.5 L) and saturated aqueous NaCl solution (800 mL), dried over Na_2SO_4 , treated with activated charcoal, filtered through Celite, and evaporated under reduced pressure. The residual solid was triturated with EtOAc/Et₂O, and collected by filtration to give 52.9 g (63%) of **63b** as pale yellow crystals: mp 123–125 °C (dec.); ¹H NMR (400 MHz, CDCl₃): δ 0.89 (s, 3H), 1.28 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 2.48–2.61 (m, 2H), 3.59–3.75 (m, 4H), 4.10–4.23 (m, 2H), 4.24–4.36 (m, 2H), 5.61 (s, 1H), 6.89 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 13.8, 22.1, 22.6, 27.6, 29.3, 30.5, 40.3, 41.8, 46.4, 63.6, 72.45, 72.49, 101.2, 103.6, 105.2, 113.6, 153.8, 156.1, 157.9, 165.8; IR (Nujol) 2217, 1741, 1664, 1609, 1463, 1228, 1202, 1143 cm⁻¹; MS (APCI) m/z 425 and 427 ([M+H]⁺); elemental analysis calcd (%) for C₁₈H₂₁BrN₂O₅: C 50.84, H 4.98, N 6.59, Br 18.79; found: C 50.89, H 4.92, N 6.39, Br 18.56.

Synthesis of *N*-substituted cyclic amino acids **33b–33n**

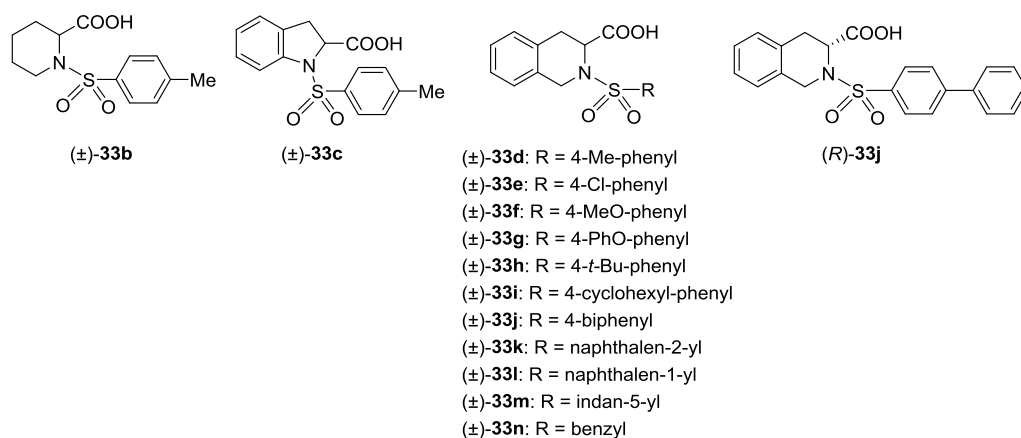
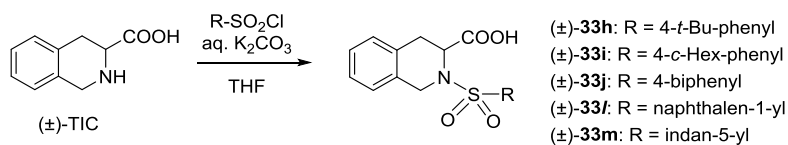


Figure S1. Structures of compounds **33b–33n**.

Compounds (±)-**33b**, (±)-**33d**, (±)-**33e**, (±)-**33f**, and (±)-**33k** were purchased from Enamine Ltd. Compounds (±)-**33c**,^[50] (±)-**33g**,^[51] and (±)-**33n**^[52] were synthesized according to the known procedure.

General procedure for synthesis of compounds (±)-**33h**, (±)-**33i**, (±)-**33j**, (±)-**33l**, and (±)-**33m**



Scheme S2. Synthesis of compounds (±)-**33h**, (±)-**33i**, (±)-**33j**, (±)-**33l**, and (±)-**33m**.

To a solution of (±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIC) (30 mmol) in 1.3 mol/L aqueous K_2CO_3 (70 mL, 91 mmol) and THF (50 mL) was added a solution of arylsulfonyl chloride (36 mmol) in THF (30 mL) dropwise over 10 minutes on an ice-water bath. The mixture was vigorously stirred for 3 hours at room temperature. EtOAc (100 mL) and water (100 mL) were added to it. The aqueous layer was separated, and the organic layer was extracted with water (100 mL). The combined aqueous extracts were washed with EtOAc (300 mL), and then acidified with 10% aqueous HCl to pH 1 on an ice bath. The resulting mixture was extracted with EtOAc. The organic extract was washed with water and saturated aqueous NaCl

solution, dried over Na₂SO₄, and then evaporated under reduced pressure to give (±)-*N*-arylsulfonyl-TIC.

Compound (±)-**33h**: colorless powder, 71%; ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.27 (s, 9H), 3.01 (dd, *J* = 6.4, 16 Hz, 1H), 3.10 (dd, *J* = 3.1, 16 Hz, 1H), 4.45 (d, *J* = 16 Hz, 1H), 4.55 (d, *J* = 16 Hz, 1H), 4.84 (dd, *J* = 3.1, 6.1 Hz, 1H), 7.08–7.16 (m, 4H), 7.55 (br d, *J* = 8.2 Hz, 2H), 7.75 (br d, *J* = 8.7 Hz, 2H), 12.85 (br, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 30.8, 31.1, 34.8, 44.0, 53.6, 126.0, 126.2, 126.5, 126.7, 126.9, 128.5, 131.3, 131.7, 136.1, 155.8, 171.6; IR (Nujol) 3291, 1741, 1695, 1331, 1178, 1155 cm⁻¹; MS (APCI) *m/z* 374 ([M+H]⁺); elemental analysis calcd (%) for C₂₀H₂₃NO₄S•0.2H₂O: C 63.71, H 6.25, N 3.71, S 8.50; found: C 63.76, H 6.15, N 3.64, S 8.31.

Compound (±)-**33i**: pale yellow crystals, 73%; mp 199–201 °C (EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.10–1.50 (m, 5H), 1.64–1.88 (m, 5H), 2.50–2.62 (m, 1H), 3.00 (dd, *J* = 6.4, 16 Hz, 1H), 3.09 (dd, *J* = 3.1, 16 Hz, 1H), 4.46 (d, *J* = 16 Hz, 1H), 4.54 (d, *J* = 16 Hz, 1H), 4.83 (dd, *J* = 3.1, 6.7 Hz, 1H), 7.09–7.16 (m, 4H), 7.38 (br d, *J* = 8.7 Hz, 2H), 7.73 (br d, *J* = 8.2 Hz, 2H), 12.84 (br, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 25.4, 26.1, 31.1, 33.45, 33.47, 43.5, 44.0, 53.6, 126.1, 126.5, 126.7, 127.1, 127.4, 128.5, 131.2, 131.7, 136.5, 152.7, 171.6; IR (Neat) 3300, 1742, 1172, 1153, 839, 750 cm⁻¹; MS (ESI) *m/z* 398 ([M-H]⁻); elemental analysis calcd (%) for C₂₂H₂₅NO₄S: C 66.14, H 6.31, N 3.51, S 8.03; found: C 66.20, H 6.20, N 3.52, S 8.22.

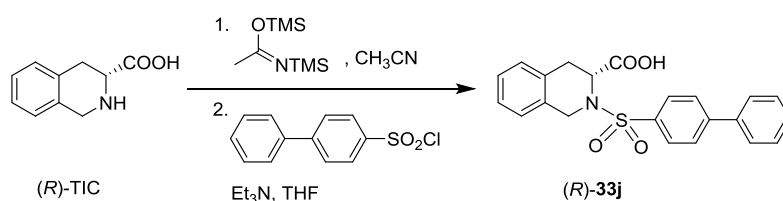
Compound (±)-**33j**: colorless crystals, 64%; mp 193–194.5 °C (CHCl₃/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆), ¹³C NMR (100 MHz, DMSO-*d*₆), and IR (Nujol), see: (**R**)-**33j**; MS (ESI) *m/z* 392 ([M-H]⁻); elemental analysis calcd (%) for C₂₂H₁₉NO₄S: C 67.16, H 4.87, N 3.56, S 8.15; found: C 66.12, H 4.58, N 3.54, S 8.14.

Compound (±)-**33l**: colorless crystals, 74%; mp 218–220 °C (THF/EtOAc); ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.05 (dd, *J* = 6.7, 16 Hz, 1H), 3.19 (dd, *J* = 2.7, 16 Hz, 1H), 4.50 (d, *J* = 16 Hz, 1H), 4.59 (d, *J* = 16 Hz, 1H), 5.10 (dd, *J* = 2.1, 6.7 Hz, 1H), 7.11 (br, 4H), 7.61–7.76 (m, 3H), 8.05–8.10 (m, 1H), 8.22–8.30 (m, 2H), 8.57 (br d, *J* = 8.2 Hz, 1H), 12.94 (br, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 31.1, 43.7, 53.1, 124.3, 124.5, 126.2, 126.5, 126.6, 126.9, 127.7, 128.2, 128.7, 129.1, 129.8, 130.9, 131.2, 134.0, 134.1, 134.4, 171.5; IR (Neat) 1723, 1592, 1506, 1499, 1266, 1214, 1161, 1047, 809, 768, 750 cm⁻¹; MS (APCI) *m/z* 368 ([M+H]⁺); elemental analysis calcd (%) for

C₂₀H₁₇NO₄S: C 65.38, H 4.66, N 3.81, S 8.73; found: C 65.63, H 4.57, N 3.71, S 8.79.

Compound (±)-**33m**: colorless crystals, 52%; mp 126–136 °C (EtOAc/*n*-hexane); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.96–2.08 (m, 2H), 2.80–2.95 (m, 4H), 2.99 (dd, *J* = 6.7, 16 Hz, 1H), 3.08 (dd, *J* = 3.3, 16 Hz, 1H), 4.46 (d, *J* = 16 Hz, 1H), 4.54 (d, *J* = 16 Hz, 1H), 4.81 (dd, *J* = 3.1, 6.7 Hz, 1H), 7.07–7.17 (m, 4H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.56–7.61 (m, 1H), 7.66 (br, 1H), 12.91 (br 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 24.9, 31.1, 32.1, 32.3, 44.1, 53.5, 122.8, 124.8, 125.3, 126.2, 126.5, 126.7, 128.5, 131.3, 131.8, 136.9, 145.1, 149.4, 171.7; IR (Nujol) 3297, 1743, 1457, 1333, 1172, 1150 cm⁻¹; MS (APCI) *m/z* 358 ([M+H]⁺); elemental analysis calcd (%) for C₁₉H₁₉NO₄S: C 63.85, H 5.36, N 3.92, S 8.97; found: C 63.81, H 5.33, N 3.86, S 8.72.

Synthesis of compound (*R*)-**33j**



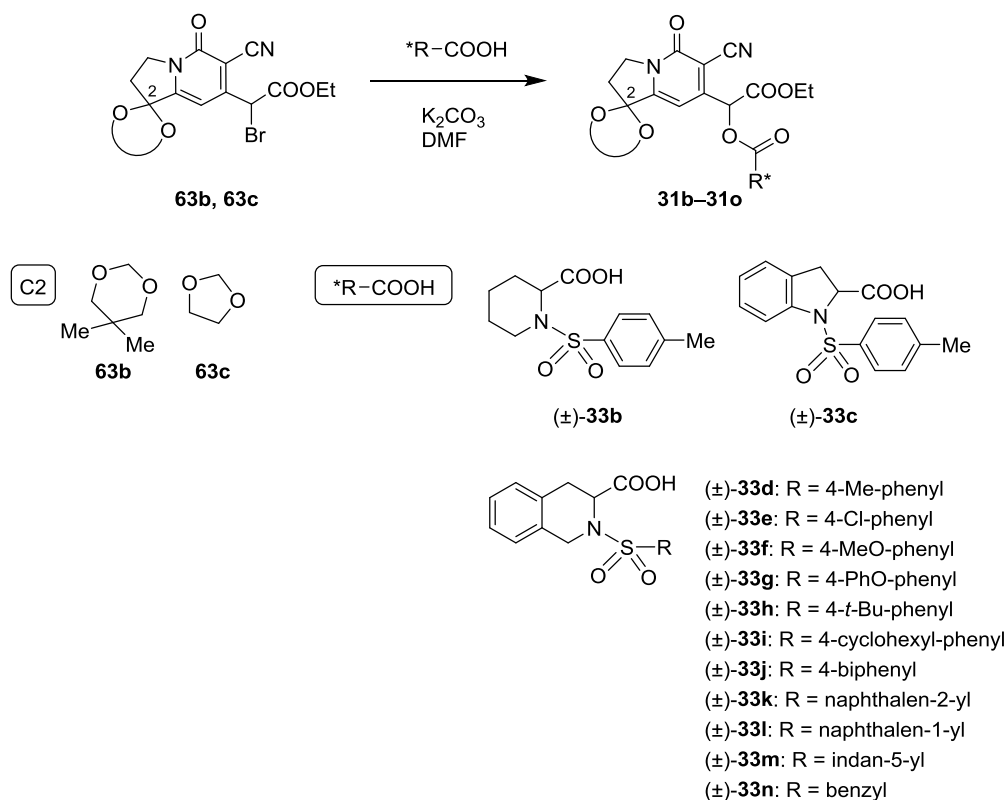
Scheme S3. Synthesis of (*R*)-**33j**.

To a suspension of (*R*)-TIC^[53] (30.2 g, 0.17 mol) in CH₃CN (300 mL) was added *N,O*-bis(trimethylsilyl)acetamide (60 mL, 0.18 mol) at room temperature under an argon atmosphere. The mixture was stirred for 1.5 hours at room temperature to afford a pale yellow solution. To the solution was added Et₃N (18.2 g, 0.18 mol) at 5 °C, and then a solution of 4-biphenylsulfonyl chloride (44.0 g, 0.17 mol) in CH₃CN (50 mL)-THF (200 mL) was added dropwise to it over 35 minutes at the same temperature. Stirring was continued and the mixture was allowed to warm to room temperature. After 16 hours, the reaction mixture was poured into ice-water (1 L), and then the pH was adjusted to pH 1 with 10% aqueous HCl. The mixture was extracted with EtOAc (2 × 1 L). The combined organic extracts were washed with water (2 × 1 L) and saturated aqueous NaCl solution (1 L), dried over Na₂SO₄, treated with activated charcoal (15 g), filtered through Celite, and then evaporated under reduced pressure. The residual solid was dissolved in hot EtOAc (500 mL) and diluted with *n*-hexane (400 mL). Separated crystals were collected by filtration, washed with 1:1 *n*-hexane/EtOAc (150 mL), and dried under reduced pressure to give

57.5 g (86%) of (*R*)-**33j** as colorless crystals: mp 203–204 °C; $[\alpha]_D^{24} = +5.78$ (*c* 1.0, DMF); $^1\text{H NMR}$ (400 MHz, DMSO-*d*₆): δ 3.06 (dd, *J* = 6.4, 16 Hz, 1H), 3.12 (dd, *J* = 3.3, 16 Hz, 1H), 4.51 (d, *J* = 16 Hz, 1H), 4.62 (d, *J* = 16 Hz, 1H), 4.90 (dd, *J* = 3.1, 6.1 Hz, 1H), 7.11–7.20 (m, 4H), 7.40–7.54 (m, 3H), 7.69–7.75 (m, 2H), 7.85 (br d, *J* = 8.7 Hz, 2H), 7.92 (br d, *J* = 8.2 Hz, 2H), 12.91 (br, 1H); $^{13}\text{C NMR}$ (100 MHz, DMSO-*d*₆): δ 31.2, 44.1, 53.6, 126.2, 126.5, 126.7, 127.1, 127.3, 127.7, 128.6, 129.2, 131.2, 131.6, 137.7, 138.4, 144.3, 171.6; IR (Nujol) 3301, 1743, 1593, 1331, 1282, 1172, 1153 cm^{-1} ; MS (APCI) *m/z* 394 ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for C₂₂H₁₉NO₄S: C 67.16, H 4.87, N 3.56, S 8.15; found: C 67.14, H 4.72, N 3.45, S 8.19. SUMICHIRAL OA-3100 column (4.6 mm × 250 mm); 20 mM AcONH₄ in CH₃OH; 1.0 mL/min; 270 nm detector; (*R*)-**12**, 37.2 min ; (*S*)-**12**, 46.1 min.

Synthesis of diester **31**

Table S1. Synthesis of diesters **31b–31o**.



Entry	α -bromo ester	R*-COOH	31	Yield (%)
1	63c	(\pm)- 33b	31b	93
2	63c	(\pm)- 33c	31c	90
3	63c	(\pm)- 33d	31d	84
4	63b	(\pm)- 33d	31e	96
5	63b	(\pm)- 33e	31f	90
6	63b	(\pm)- 33f	31g	88
7	63b	(\pm)- 33g	31h	67
8	63b	(\pm)- 33h	31i	91
9	63b	(\pm)- 33i	31j	93
10	63b	(\pm)- 33j	31k	91
11	63b	(\pm)- 33k	31l	98
12	63b	(\pm)- 33l	31m	93
13	63b	(\pm)- 33m	31n	86
14	63b	(\pm)- 33n	31o	88

Reactions were performed with bromide **63b** or **63c** (2.0 mmol), (\pm)-*N*-substituted-cyclic amino acid (**33b–33n**) (3.0 mmol) and K₂CO₃ (1.8 mmol) in DMF at 60°C.

General procedure for synthesis of **31**

To a solution of α -bromo ester (**63b** or **63c**) (2.0 mmol) and (\pm)-*N*-substituted-cyclic amino acid (**33b–33n**) (3.0 mmol) in DMF (8 mL) was added K₂CO₃ (1.8 mmol) at room temperature under an argon atmosphere. The mixture was stirred for 45 minutes at 60 °C, and then cooled in an ice bath. To it were added EtOAc, saturated aqueous NaHCO₃, and water. The resulting mixture was extracted with EtOAc. The organic extract was washed with water and saturated aqueous NaCl solution, dried over Na₂SO₄, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Fuji Silysia, BW-300, 32–53 μ m) to give diesters **31b–31o** (mixture of diastereo isomers).

Diester **31b**: pale yellow foam, 93%; ¹H NMR (400 M Hz, CDCl₃): δ 1.26 and 1.30 (2 \times t, *J* = 7.4 Hz, 3H), 1.35–1.51 (m, 2H), 1.51–1.82 (m, 3H), 2.19–2.32 (m, 1H), 2.42 and 2.43 (2 \times s, 3H), 2.38–2.48 (m, 2H), 3.17– 3.47 (m, 1H), 3.68–3.79 (m, 1H), 4.05–4.40 (m, 8H), 4.89–4.96 (m, 1H), 6.07 and 6.29 (2 \times s, 1H), 6.49 and 6.69 (2 \times s, 1H),

7.22–7.31 (m, 2H), 7.59–7.72 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.85, 13.89, 14.2, 19.6, 20.0, 21.0, 21.5, 24.2, 24.4, 27.0, 27.3, 33.51, 33.54, 42.6, 42.8, 45.7, 45.9, 54.5, 55.1, 60.4, 63.1, 63.2, 65.6, 65.9, 66.2, 66.3, 71.7, 71.9, 97.8, 97.9, 103.9, 104.1, 112.9, 113.0, 113.5, 113.7, 126.9, 129.6, 129.7, 136.6, 137.6, 143.5, 143.8, 153.5, 153.7, 154.4, 154.5, 158.2, 165.31, 165.36, 169.0, 169.3, 171.1; IR (Nujol) 2225, 1749, 1663, 1607 cm^{-1} ; MS (APCI) m/z 586 ($[\text{M}+\text{H}]^+$).

Diester **31c**: colorless foam, 90%; ^1H NMR (400 MHz, CDCl_3): δ 1.19 and 1.30 ($2 \times \text{t}$, $J = 7.1$ Hz, 3H), 2.37 and 2.38 ($2 \times \text{s}$, 3H), 2.41–2.49 (m, 2H), 3.07 and 3.22 ($2 \times \text{dd}$, $J = 11, 16$ Hz, 1H), 3.32 and 3.36 ($2 \times \text{dd}$, $J = 3.3, 16$ Hz and 4.6, 16 Hz, 1H), 4.05–4.42 (m, 8H), 4.89 and 5.03 ($2 \times \text{dd}$, $J = 4.6, 11$ Hz and 3.3, 11 Hz, 1H), 6.23 and 6.32 ($2 \times \text{s}$, 1H), 6.53 and 6.78 ($2 \times \text{s}$, 1H), 7.00–7.15 (m, 2H), 7.18–7.25 (m, 3H), 7.53–7.66 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.9, 21.5, 31.9, 32.6, 33.4, 45.8, 62.0, 62.2, 63.14, 63.3, 65.6, 65.7, 66.2, 66.3, 71.9, 72.6, 97.7, 98.2, 103.5, 103.7, 112.89, 112.92, 113.66, 113.71, 115.3, 116.5, 124.6, 125.0, 125.2, 127.1, 128.1, 129.7, 129.81, 129.84, 130.1, 134.1, 134.4, 140.8, 141.1, 144.6, 144.7, 153.7, 153.8, 154.4, 154.5, 158.2, 158.3, 164.9, 165.2, 169.0, 169.4; IR (Nujol) 2225, 1751, 1661, 1607, 1537, 1310, 1167, 1089, 1037, 757 cm^{-1} ; MS (APCI) m/z 620 ($[\text{M}+\text{H}]^+$).

Diester **31d**: colorless foam, 84%; ^1H NMR (400 MHz, CDCl_3): δ 1.18 and 1.19 ($2 \times \text{t}$, $J = 7.1$ Hz, 3H), 2.38–2.48 (m, 5H), 3.07–3.22 (m, 1H), 3.25–3.36 (m, 1H), 4.02–4.40 (m, 8H), 4.47–4.81 (m, 2H), 5.15–5.22 (m, 1H), 5.98 and 6.15 ($2 \times \text{s}$, 1H), 6.54 and 6.66 ($2 \times \text{s}$, 1H), 7.00–7.2 (m, 4H), 7.22–7.28 (m, 2H), 7.65–7.73 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 21.5, 31.0, 31.2, 33.49, 33.52, 44.3, 44.5, 45.7, 45.8, 53.6, 53.8, 63.1, 65.7, 65.9, 66.2, 72.0, 72.1, 97.8, 97.9, 103.79, 103.83, 112.9, 113.0, 113.5, 113.6, 126.16, 126.18, 126.9, 127.96, 127.05, 127.09, 127.15, 127.19, 128.7, 128.9, 129.7, 129.8, 130.37, 130.41, 131.0, 131.1, 135.6, 136.1, 143.9, 144.1, 153.6, 153.8, 154.5, 158.2, 164.9, 165.0, 168.8; IR (Nujol) 2225, 1750, 1663, 1457, 1198, 1161 cm^{-1} ; MS (APCI) m/z 696 ($[\text{M}+\text{H}]^+$).

Diester **31e**: colorless foam, 93%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 and 0.91 ($2 \times \text{s}$, 3H), 1.10 and 1.19 ($2 \times \text{t}$, $J = 6.9, 7.2$ Hz, 3H), 1.34 and 1.36 ($2 \times \text{s}$, 3H), 2.38 and 2.40 ($2 \times \text{s}$, 3H), 2.45–2.65 (m, 2H), 3.18–3.40 (m, 2H), 3.60–3.80 (m, 4H), 3.95–4.24 (m, 4H), 4.54 and 4.60 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 4.70 and 4.72 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 5.11–5.27 (m, 1H), 5.94 and 5.95 ($2 \times \text{s}$, 1H), 6.57 and 6.58 ($2 \times \text{s}$, 1H), 7.00–7.26 (m, 6H), 7.65–7.73 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 21.5, 22.1, 22.7, 22.8,

29.1, 29.2, 30.49, 30.51, 31.8, 31.9, 44.4, 44.5, 46.5, 46.6, 53.3, 53.7, 62.90, 62.93, 71.8, 72.0, 72.5, 72.6, 98.8, 98.9, 104.3, 105.3, 105.4, 113.39, 113.42, 126.07, 126.11, 126.9, 127.0, 127.3, 127.4, 128.7, 128.8, 129.6, 129.7, 130.16, 130.20, 131.2, 131.4, 135.3, 135.8, 143.7, 144.0, 153.56, 153.66, 154.0, 154.1, 158.0, 158.1, 164.8, 164.9, 168.6, 168.9; IR (ATR) 2226, 1748, 1662, 1614, 1455, 1203, 1159 cm^{-1} ; MS (APCI) m/z 676 ($[\text{M}+\text{H}]^+$).

Diester **31f**: colorless foam, 85%; ^1H NMR (400 MHz, CDCl_3): δ 0.89 and 0.90 ($2 \times \text{s}$, 3H), 1.11 and 1.20 ($2 \times \text{t}$, $J = 6.9$ and 7.2 Hz, 3H), 1.33 and 1.36 ($2 \times \text{s}$, 3H), 2.48–2.65 (m, 2H), 3.21–3.44 (m, 2H), 3.60–3.75 (m, 4H), 3.96–4.26 (m, 4H), 4.51 and 4.59 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 4.69 and 4.74 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 5.16 and 5.26 ($2 \times \text{dd}$, $J = 3.1$, 6.2 and 3.6, 5.1 Hz, 1H), 5.96 and 5.99 ($2 \times \text{s}$, 1H), 6.54 and 6.56 ($2 \times \text{s}$, 1H), 7.00–7.21 (m, 4H), 7.38–7.45 (m, 2H), 7.72–7.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 22.1, 22.7, 22.8, 29.0, 29.1, 30.48, 30.51, 31.8, 31.9, 44.4, 44.5, 46.6, 46.7, 53.7, 53.8, 62.96, 63.03, 72.0, 72.1, 72.5, 72.56, 72.58, 98.8, 99.0, 104.3, 105.35, 105.4, 113.37, 113.42, 126.1, 127.0, 127.1, 128.76, 128.82, 128.9, 129.27, 129.35, 130.0, 130.3, 130.9, 131.1, 137.1, 137.3, 139.2, 139.5, 153.3, 153.6, 154.07, 154.12, 158.0, 158.1, 164.8, 164.9, 168.58, 168.64; IR (ATR) 2226, 1749, 1662, 1615, 1475, 1203, 1163 cm^{-1} ; MS (APCI) m/z 696 and 698 ($[\text{M}+\text{H}]^+$).

Diester **31g**: yellow foam, 88%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 and 0.91 ($2 \times \text{s}$, 3H), 1.11 and 1.15 ($2 \times \text{t}$, $J = 7.2$ Hz, 3H), 1.34 and 1.37 ($2 \times \text{s}$, 3H), 2.47–2.66 (m, 2H), 3.25–3.36 (m, 2H), 3.60–3.80 (m, 4H), 3.84 and 3.85 ($2 \times \text{s}$, 3H), 3.96–4.24 (m, 4H), 4.54 and 4.59 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 4.70 and 4.75 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 5.14 and 5.24 ($2 \times \text{dd}$, $J = 4.2$, 5.1 and 3.1, 6.1 Hz, 1H), 5.92 and 5.95 ($2 \times \text{s}$, 1H), 6.49 and 6.56 ($2 \times \text{s}$, 1H), 6.81–6.92 (m, 2H), 7.03–7.21 (m, 4H), 7.70–7.76 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 22.1, 22.7, 22.8, 29.06, 29.13, 30.48, 30.51, 31.8, 32.1, 44.35, 44.41, 46.5, 46.6, 53.3, 53.7, 55.7, 62.9, 71.8, 72.04, 72.5, 72.6, 98.8, 98.9, 104.25, 104.33, 105.31, 105.37, 113.5, 114.0, 114.2, 126.0, 126.1, 126.9, 127.0, 128.7, 128.9, 129.42, 129.44, 129.9, 130.21, 130.24, 130.28, 131.3, 131.4, 153.4, 153.7, 154.0, 154.1, 157.9, 158.1, 162.9, 163.1, 164.7, 164.9, 168.6, 169.1; IR (Neat) 2225, 1750, 1664, 1261, 1158, 756 cm^{-1} ; MS (APCI) m/z 692 ($[\text{M}+\text{H}]^+$).

Diester **31h**: pale yellow foam, 67%; ^1H NMR (400 MHz, CDCl_3): δ 0.89 and 0.91 ($2 \times \text{s}$, 3H), 1.13 and 1.17 ($2 \times \text{t}$, $J = 7.2$ Hz, 3H), 1.33 and 1.36 ($2 \times \text{s}$, 3H), 2.47–2.62 (m, 2H), 3.20–3.45 (m, 2H), 3.60–3.76 (m, 4H), 4.00–4.24 (m, 4H), 4.54 and 4.61 ($2 \times \text{d}$, J

= 15 and 16 Hz, 1H), 4.68 and 4.72 (2 × d, J = 15 and 16 Hz, 1H), 5.16 and 5.24 (2 × dd, J = 3.3, 6.4 and 3.6, 5.1 Hz, 1H), 6.00 and 6.01 (2 × s, 1H), 6.58 and 6.61 (2 × s, 1H), 6.91–6.99 (m, 2H), 7.02–7.26 (m, 7H), 7.36–7.44 (m, 2H), 7.72–7.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.76, 13.81, 22.08, 22.1, 22.7, 22.8, 29.1, 29.2, 30.49, 30.51, 31.82, 31.9, 44.36, 44.46, 46.55, 46.61, 53.6, 53.8, 62.96, 62.99, 71.96, 72.02, 72.53, 72.57, 98.8, 98.9, 104.3, 104.4, 105.3, 105.4, 113.4, 117.6, 117.7, 120.2, 120.3, 124.8, 124.9, 126.1, 126.95, 126.97, 127.01, 128.7, 128.8, 129.5, 129.6, 130.1, 130.15, 130.21, 130.4, 131.2, 131.4, 132.1, 132.4, 153.5, 153.7, 154.0, 154.1, 155.1, 155.3, 158.0, 158.1, 161.6, 161.8, 164.9, 168.7, 168.8; IR (Nujol) 2225, 1751, 1664, 1614, 1582, 1242, 1157, 1090, 1055, 755 cm^{-1} ; MS (APCI) m/z 754 ($[\text{M}+\text{H}]^+$).

Diester **31i**: colorless foam, 91%; ^1H NMR (400 MHz, CDCl_3): δ 0.91 (s, 3H), 1.12 and 1.22 (2 × t, J = 7.1 Hz, 3H), 1.30 and 1.31 (2 × s, 9H), 1.34 (s, 3H), 2.46–2.65 (m, 2H), 3.14–3.42 (m, 2H), 3.62–3.76 (m, 4H), 4.00–4.28 (m, 4H), 4.50–4.71 (m, 2H), 5.17 and 5.23 (2 × dd, J = 3.1, 6.2 and 3.3, 5.9 Hz, 1H), 6.01 and 6.08 (2 × s, 1H), 6.63 and 6.73 (2 × s, 1H), 7.00–7.19 (m, 4H), 7.42–7.48 (m, 2H), 7.69–7.78 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 13.9, 22.1, 22.2, 22.7, 29.2, 29.4, 30.51, 30.52, 31.0, 31.5, 31.7, 35.09, 35.1, 44.4, 44.5, 46.5, 46.6, 53.6, 53.8, 62.9, 63.0, 71.9, 72.0, 72.5, 98.95, 99.04, 104.2, 104.3, 105.3, 105.4, 113.4, 113.5, 125.98, 126.04, 126.13, 126.2, 126.89, 126.92, 127.0, 127.1, 127.2, 128.7, 130.37, 130.44, 131.4, 131.5, 135.5, 135.9, 153.75, 153.84, 154.0, 154.1, 156.6, 156.8, 158.1, 158.2, 164.9, 165.0, 168.77, 168.81; IR (Nujol) 2225, 1753, 1665, 1615, 1595, 1353, 1164 cm^{-1} ; MS (APCI) m/z 718 ($[\text{M}+\text{H}]^+$).

Diester **31j**: pale yellow foam, 93%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (s, 3H), 1.11 and 1.22 (2 × t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.20–1.50 (m, 5H), 1.50–1.95 (m, 5H), 2.46–2.67 (m, 3H), 3.15–3.42 (m, 2 H), 3.63–3.76 (m, 4H), 3.96–4.28 (m, 4H), 4.52–4.70 (m, 2H), 5.16 and 5.22 (2 × dd, J = 3.1, 6.7 and 3.3, 5.9 Hz, 1H), 5.99 and 6.06 (2 × s, 1H), 6.62 and 6.70 (2 × s, 1H), 7.00–7.20 (m, 4H), 7.23–7.29 (m, 2H), 7.68–7.77 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 22.10, 22.14, 22.7, 25.9, 26.6, 29.2, 29.4, 30.5, 30.52, 31.6, 31.7, 33.93, 33.99, 34.04, 34.1, 44.38, 44.42, 44.5, 46.5, 46.6, 53.5, 53.8, 62.9, 63.0, 71.9, 72.0, 72.5, 98.9, 99.0, 104.3, 105.3, 105.4, 113.5, 126.1, 126.2, 126.88, 126.93, 127.3, 127.46, 127.52, 128.69, 128.73, 130.3, 131.36, 131.43, 135.6, 136.1, 153.5, 153.7, 153.8, 154.0, 154.1, 158.1, 164.90, 164.94, 168.7, 168.8; IR (Nujol) 2224, 1752, 1665, 1614, 1161, 1091, 1055, 967, 753 cm^{-1} ; MS (APCI) m/z 744 ($[\text{M}+\text{H}]^+$).

Diester **31k**: ^1H NMR (400 MHz, $\text{DMSO-}d_6$), ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$), and IR (Nujol), see: diester (*R*)-**31k**.

Diester **31l**: yellow viscous oil, 92%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 and 0.91 ($2 \times \text{s}$, 3H), 1.07 and 1.08 ($2 \times \text{t}$, $J = 6.9$ Hz, 3H), 1.34 and 1.38 ($2 \times \text{s}$, 3H), 2.40–2.67 (m, 2H), 3.20–3.43 (m, 2H), 3.56–3.83 (m, 4H), 3.88–4.25 (m, 4H), 4.60 and 4.64 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 4.77 and 4.86 ($2 \times \text{d}$, $J = 15$ Hz, 1H), 5.22 and 5.35 ($2 \times \text{dd}$, $J = 3.1, 6.7$ and 3.1, 62 Hz, 1H), 5.76 and 5.87 ($2 \times \text{s}$, 1H), 6.35 and 6.57 ($2 \times \text{s}$, 1H), 6.96–7.22 (m, 4H), 7.50–7.60 (m, 1H), 7.60–7.68 (m, 1H), 7.71–7.79 (m, 1H), 7.84–7.94 (m, 3H), 8.36–8.44 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 14.2, 21.0, 22.1, 22.6, 22.7, 22.9, 29.0, 29.2, 30.5, 31.7, 32.3, 36.4, 44.6, 46.4, 46.6, 53.5, 53.9, 60.4, 62.8, 62.9, 71.8, 72.1, 72.50, 72.54, 72.6, 98.4, 98.9, 104.1, 104.3, 105.2, 105.4, 113.3, 122.4, 122.5, 126.0, 126.1, 126.3, 126.9, 127.0, 127.3, 127.5, 127.96, 128.00, 128.66, 128.73, 128.88, 128.94, 128.98, 129.05, 129.08, 129.3, 129.5, 130.16, 130.25, 131.1, 131.3, 131.8, 132.0, 134.7, 134.9, 135.36, 135.41, 152.9, 153.5, 153.7, 154.0, 157.6, 158.1, 164.5, 164.8, 168.6, 169.1; IR (ATR) 2225, 1747, 1661, 1614, 1203, 1157 cm^{-1} ; MS (APCI) m/z 712 ($[\text{M}+\text{H}]^+$).

Diester **31m**: yellow foam, 93%; ^1H NMR (400 MHz, CDCl_3): δ 0.89 and 0.91 ($2 \times \text{s}$, 3H), 1.08 and 1.15 ($2 \times \text{t}$, $J = 7.1$ Hz, 3H), 1.32 and 1.35 ($2 \times \text{s}$, 3H), 2.49–2.66 (m, 2H), 3.21–3.46 (m, 2H), 3.65–3.78 (m, 4H), 3.95–4.24 (m, 4H), 4.58–4.85 (m, 2H), 5.33 and 5.39 ($2 \times \text{dd}$, $J = 2.3, 6.4$ and 2.6, 6.1 Hz, 1H), 5.85 and 5.86 ($2 \times \text{s}$, 1H), 6.60 and 6.65 ($2 \times \text{s}$, 1H), 6.95–7.06 (m, 1H), 7.07–7.16 (m, 3H), 7.47–7.61 (m, 3H), 7.87–7.94 (m, 1H), 8.02–8.08 (m, 1H), 8.27–8.34 (m, 1H), 8.57–8.67 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 22.1, 22.2, 22.7, 29.2, 29.4, 30.5, 31.57, 31.61, 44.26, 44.31, 46.4, 46.6, 53.2, 53.5, 62.9, 71.97, 72.03, 72.5, 99.0, 99.3, 104.2, 104.3, 105.3, 105.4, 113.4, 124.0, 124.1, 124.38, 124.44, 126.0, 126.1, 126.8, 126.85, 126.89, 128.1, 128.2, 128.47, 128.5, 128.8, 128.9, 129.0, 129.1, 130.1, 130.2, 130.3, 130.4, 130.98, 131.01, 133.7, 133.9, 134.25, 134.34, 134.6, 134.8, 153.3, 153.5, 153.8, 154.0, 158.0, 158.2, 164.7, 164.9, 168.7, 169.0; IR (Nujol) 2225, 1749, 1663, 1613, 1203, 1161, 1142, 1056, 759 cm^{-1} ; MS (APCI) m/z 712 ($[\text{M}+\text{H}]^+$).

Diester **31n**: colorless foam, 86%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 and 0.91 ($2 \times \text{s}$, 3H), 1.10 and 1.19 ($2 \times \text{t}$, $J = 7.1$ Hz, 3H), 1.34 and 1.36 ($2 \times \text{s}$, 3H), 2.05–2.16 (m, 2H), 2.47–2.64 (m, 2H), 2.83–3.00 (m, 4H), 3.24–3.42 (m, 2H), 3.65–3.76 (m, 4H),

3.95–4.24 (m, 4H), 4.56 and 4.63 (2 × d, $J = 15$ Hz, 1H), 4.68 and 4.70 (2 × d, $J = 15$ Hz, 1H), 5.14 and 5.22 (dd and t, $J = 3.1, 62$ Hz and $J = 4.6$ Hz, 1H), 5.96 and 5.97 (2 × s, 1H), 6.60 and 6.61 (2 × s, 1H), 7.02–7.25 (m, 5H), 7.54–7.66 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 14.2, 21.0, 22.1, 22.7, 22.8, 25.1, 25.3, 29.2, 29.3, 30.50, 30.51, 31.8, 31.9, 32.56, 32.60, 32.80, 32.83, 44.4, 44.5, 46.5, 46.6, 53.4, 53.7, 60.4, 62.9, 71.8, 72.0, 72.5, 98.8, 99.0, 104.2, 105.3, 105.4, 113.4, 123.18, 123.23, 124.7, 125.55, 125.64, 126.1, 126.8, 126.9, 128.7, 128.8, 130.3, 131.4, 131.5, 136.1, 136.5, 145.4, 145.6, 150.1, 150.4, 153.7, 154.0, 154.1, 158.0, 158.2, 164.8, 164.9, 168.7, 168.9; IR (Nujol) 2225, 1750, 1665, 1457, 1146, 1057 cm^{-1} ; MS (APCI) m/z 702 ($[\text{M}+\text{H}]^+$).

Diester **31o**: colorless foam, 88%; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (s, 3H), 1.13 and 1.23 (2 × t, $J = 7.1$ Hz, 3H), 1.31 (s, 3H), 2.50–2.58 (m, 2H), 3.03 and 3.14 (2 × dd, $J = 6.7, 16$ Hz, 1H), 3.20 and 3.33 (2 × dd, $J = 2.8, 16$ and $3.3, 16$ Hz, 1H), 3.61–3.70 (m, 4H), 4.00–4.62 (m, 8H), 4.91 and 4.97 (2 × dd, $J = 3.3, 6.4$ and $2.8, 6.4$ Hz, 1H), 6.14 and 6.18 (2s, 1H), 6.57 and 6.68 (2s, 1H), 6.95–7.03 (m, 1H), 7.05–7.23 (m, 3H), 7.28–7.42 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.76, 13.83, 22.1, 22.13, 22.76, 29.2, 29.3, 30.5, 31.2, 31.6, 45.05, 45.11, 46.5, 46.6, 54.4, 54.5, 58.46, 58.53, 63.0, 63.2, 72.2, 72.5, 98.9, 99.2, 104.3, 104.4, 105.3, 105.4, 113.5, 126.0, 126.1, 126.96, 127.0, 127.11, 127.14, 128.7, 128.8, 130.5, 130.8, 130.89, 130.92, 131.5, 131.7, 153.5, 153.7, 154.11, 154.14, 158.08, 158.14, 164.9, 165.1, 169.4, 169.5; IR (Nujol) 2225, 1751, 1663, 1613, 1541, 1151, 1057, 756 cm^{-1} ; MS (APCI) m/z 676 ($[\text{M}+\text{H}]^+$).

Diastereoselective ethylation of diester **31**

General procedure for diastereoselective ethylation of **31** to **32**

To a solution of diester **31** (1.2 mmol) in 7 mL of DMF was added NaH (60% oil suspension, 1.4 mmol) at 6 °C under an Ar atmosphere. The mixture was stirred for 1 hour at room temperature, then iodoethane (12 mmol) was added dropwise to it over 5 minutes at 6 °C. Stirring was continued and the mixture was allowed to warm to room temperature. After 19 hours, the reaction mixture was poured into ice-cooled 10% aqueous citric acid. The resulting mixture was extracted with EtOAc. The organic extract was washed with water and saturated aqueous NaCl solution, dried over Na_2SO_4 , and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Fuji Silysia, BW-300, 32–53 μm) to give a mixture of compounds **32** and **67**. The ratio of compounds **32:67** was determined by

¹H NMR spectroscopy from the relative intensities of the signals in the range $\delta = 6.40$ – 6.80 ppm, which signals were shown below in bold italic.

N-Tosylpipicolinic acid ester **32b**: pale yellow foam, 82%; ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, $J = 7.5$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.20–1.45 (m, 2H), 1.56–1.78 (m, 3H), 2.26–2.36 (m, 1H), 2.42 (s, 3H), 2.40–2.47 (m, 2H), 2.48–2.68 (m, 2H), 3.28–3.38 (m, 1H), 3.67–3.81 (m, 1H), 4.05–4.35 (m, 8H), 4.90–4.97 (m, 1H), **6.55 and 6.64** ($2 \times s$, **1H**, **13.5:86.5**), 7.28 (br. d, $J = 8.2$ Hz, 2H), 7.71 (br. d, $J = 8.2$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.4, 7.6, 13.8, 19.9, 20.0, 21.5, 24.2, 24.3, 27.0, 28.4, 28.5, 33.6, 33.7, 42.7, 45.7, 54.7, 55.0, 62.8, 62.9, 65.9, 66.0, 84.9, 84.9, 97.5, 98.1, 101.5, 101.8, 113.0, 114.3, 127.0, 129.6, 129.7, 137.5, 137.7, 143.3, 153.0, 157.7, 158.2, 159.2, 167.5, 169.5; IR (Nujol) 2222, 1755, 1658, 1609 cm⁻¹; MS (APCI) m/z 614 ([M+H]⁺).

N-Tosylindoline-2-carboxylic acid ester **32c**: pale yellow foam, 90%; ¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 2.37 (br. s, 3H), 2.40–2.48 (m, 2H), 2.63 (br. q, $J = 7.4$ Hz, 2H), 3.15–3.39 (m, 2H), 4.03–4.40 (m, 8H), 5.01 and 5.08 ($2 \times dd$, $J = 5.7, 11$ Hz and $5.6, 10$ Hz, 1H), **6.62 and 6.74** ($2 \times s$, **1H**, **76.5:23.5**), 6.97–7.1 (m, 2H), 7.11–7.29 (m, 3H), 7.53–7.65 (m, 1H), 7.67–7.76 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.0, 7.5, 8.0, 13.6, 13.8, 13.9, 14.2, 15.6, 21.0, 21.5, 28.4, 29.9, 32.4, 32.6, 33.5, 33.6, 39.5, 45.7, 60.4, 61.8, 61.9, 62.5, 62.8, 63.0, 65.8, 65.9, 65.95, 66.03, 83.8, 85.2, 97.4, 97.9, 98.0, 101.7, 102.0, 110.2, 112.98, 113.06, 114.5, 114.6, 115.4, 115.6, 120.7, 123.2, 124.5, 124.6, 124.98, 125.03, 125.6, 126.1, 127.1, 127.38, 127.42, 128.1, 129.3, 129.7, 129.9, 134.0, 139.2, 141.2, 144.58, 144.63, 153.0, 157.9, 158.9, 159.2, 159.4, 160.1, 167.4, 167.6, 168.3, 168.9; IR (Nujol) 2222, 1747, 1656, 1605, 1526, 1249, 1167, 1089, 1023, 947, 815, 759 cm⁻¹; MS (APCI) m/z 648 ([M+H]⁺).

N-Tosyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32d**: colorless foam, 93%; ¹H NMR (400 MHz, CDCl₃): δ 0.71 (t, $J = 7.4$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 2.29–2.50 (m, 7H), 3.13 (dd, $J = 16, 6.9$ Hz, 1H), 3.40 (dd, $J = 16, 3.3$ Hz, 1H), 3.86–4.27 (m, 8H), 4.50–4.71 (m, 2H), 5.18 (dd, $J = 6.4, 3.3$ Hz, 1H), **6.40 and 6.57** ($2 \times s$, **1H**, **11:89**), 7.01–7.28 (m, 6H), 7.72 (d like, $J = 8.2$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.31, 13.6, 21.5, 28.9, 31.4, 33.6, 44.6, 45.7, 54.0, 62.7, 65.9, 66.0, 84.7, 97.6, 101.7, 113.0, 114.6, 126.1, 126.9, 127.0, 127.2, 128.5, 129.67, 129.72, 131.0, 131.8, 136.2, 143.5, 152.8, 157.9, 159.2, 167.3, 168.9; IR (Nujol) 2222, 1757, 1658,

1460, 1377, 1162 cm^{-1} ; MS (APCI) m/z 662 ($[\text{M}+\text{H}]^+$).

N-Tosyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32e**: yellow foam, 94%; ^1H NMR (400 MHz, CDCl_3): δ 0.64 (t, $J = 7.5$ Hz, 3H), 0.87 (s, 3H), 1.11 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 3H), 2.20–2.40 (m, 2H), 2.36 (s, 3H), 2.45–2.63 (m, 2H), 3.23 (dd, $J = 6.4, 16$ Hz, 1H), 3.50 (dd, $J = 3.2, 16$ Hz, 1H), 3.56–3.70 (m, 4H), 3.89–3.99 (m, 1H), 4.03–4.12 (m, 1H), 4.12–4.24 (m, 2H), 4.63 (m, 2H), 5.27 (dd, $J = 2.9, 6.4$ Hz, 1H), **6.47 and 6.65** ($2 \times$ s, **1H, 11.5:88.5**), 7.00–7.18 (m, 4H), 7.23 (d, $J = 8.2$ Hz, 2H), 7.73 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 13.3, 13.6, 21.4, 22.1, 22.6, 28.9, 29.2, 30.4, 32.0, 44.4, 46.4, 53.9, 62.5, 62.7, 72.4, 72.5, 84.6, 85.0, 98.3, 102.0, 105.3, 114.8, 126.2, 126.85, 126.88, 127.3, 128.6, 129.6, 129.64, 131.0, 131.8, 136.2, 143.3, 143.6, 152.7, 158.1, 159.2, 167.4, 168.7; IR (Nujol) 2222, 1757, 1659, 1615, 1531 cm^{-1} ; MS (APCI) m/z 704 ($[\text{M}+\text{H}]^+$).

N-4-Chlorobenzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32f**: colorless foam, 91%; ^1H NMR (400 MHz, CDCl_3): δ 0.69 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 3H), 1.02 (t, $J = 7.1$ Hz, 3H), 1.23 (s, 3H), 2.13–2.37 (m, 2H), 2.45–2.63 (m, 2H), 3.35 (dd, $J = 6.2, 16$ Hz, 1H), 3.50 (dd, $J = 2.8, 16$ Hz, 1H), 3.56–3.69 (m, 4H), 3.70–3.84 (m, 1H), 3.93–4.05 (m, 1H), 4.10–4.30 (m, 2H), 4.59 (d, $J = 15$ Hz, 1H), 4.74 (d, $J = 15$ Hz, 1H), 5.33 (dd, $J = 2.9, 6.4$ Hz, 1H), **6.44 and 6.74** ($2 \times$ s, **1H, 9:91**), 7.01–7.10 (m, 1H), 7.12–7.22 (m, 3H), 7.39–7.45 (m, 2H), 7.76–7.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.1, 7.5, 13.4, 13.7, 22.1, 22.6, 29.3, 29.9, 30.4, 32.2, 44.3, 46.5, 53.7, 62.7, 72.37, 72.43, 84.4, 98.4, 101.5, 105.4, 114.8, 126.1, 126.9, 127.0, 128.7, 128.7, 129.2, 130.8, 131.4, 137.6, 138.9, 152.7, 158.5, 159.2, 167.1, 168.4; IR (Nujol) 2222, 1747, 1657, 1614, 1240, 1165, 1087, 758 cm^{-1} ; MS (APCI) m/z 724 ($[\text{M}+\text{H}]^+$).

N-4-Methoxybenzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32g**: pale yellow foam, 92%; ^1H NMR (400 MHz, CDCl_3): δ 0.66 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 3H), 1.09 (t, $J = 7.2$ Hz, 3H), 1.23 (br. s, 3H), 2.18–2.40 (m, 2H), 2.48–2.60 (m, 2H), 3.26 (dd, $J = 6.4, 16$ Hz, 1H), 3.48 (dd, $J = 3.1, 16$ Hz, 1H), 3.54–3.68 (m, 4H), 3.82 (s, 3H), 3.85–3.97 (m, 1H), 4.02–4.14 (m, 1H), 4.14–4.21 (m, 2H), 4.58–4.71 (m, 2H), 5.26 (dd, $J = 3.1, 6.4$ Hz, 1H), **6.46 and 6.68** ($2 \times$ s, **1H, 10:90**), 6.88–6.94 (m, 2H), 7.01–7.08 (m, 1H), 7.10–7.20 (m, 3H), 7.76–7.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.1, 7.3, 13.7, 22.1, 22.6, 29.1, 29.2, 30.4, 32.0, 44.4, 46.4, 53.8, 55.5, 62.7, 72.4, 72.5, 84.5, 98.4, 101.9, 105.3, 114.1, 114.8, 126.1, 126.85, 126.87, 128.6, 129.5, 130.9, 131.0, 131.9, 152.6, 158.2, 159.2, 162.8, 167.4, 168.7; IR (Nujol)

2223, 1757, 1747, 1659, 1259, 1158, 1093, 967, 835, 759 cm^{-1} ; MS (APCI) m/z 720 ($[\text{M}+\text{H}]^+$).

N-4-Phenoxybenzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32h**: colorless foam, 88%; ^1H NMR (400 MHz, CDCl_3): δ 0.68 (t, $J = 7.4$ Hz, 3H), 0.86 (br. s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H), 1.24 (br. s, 3H), 2.21–2.38 (m, 2H), 2.40–2.57 (m, 2H), 3.31 (dd, $J = 6.4, 16$ Hz, 1H), 3.49 (dd, $J = 3.1, 16$ Hz, 1H), 3.55–3.68 (m, 4H), 3.81–3.93 (m, 1H), 4.01–4.11 (m, 1H), 4.15 (t like, $J = 6.9$ Hz, 2H), 4.62 (d, $J = 15$ Hz, 1H), 4.67 (d, $J = 15$ Hz, 1H), 5.28 (dd, $J = 3.1, 6.4$ Hz, 1H), **6.46 and 6.70** ($2 \times$ s, **1H, 10:90**), 6.90–7.09 (m, 5H), 7.12–7.24 (m, 4H), 7.34–7.44 (m, 2H), 7.76–7.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.4, 13.7, 22.1, 22.6, 29.1, 29.3, 30.4, 32.1, 44.5, 46.5, 53.9, 62.7, 72.35, 72.43, 84.5, 98.4, 101.8, 105.3, 114.8, 117.6, 117.7, 120.1, 124.7, 126.2, 126.9, 128.6, 129.5, 130.1, 131.1, 131.8, 132.8, 152.7, 155.3, 158.3, 159.2, 161.4, 167.3, 168.7; IR (Nujol) 2222, 1760, 1747, 1659, 1243, 1157, 1091, 1060, 754 cm^{-1} ; MS (APCI) m/z 782 ($[\text{M}+\text{H}]^+$).

N-4-*tert*-Butylbenzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32i**: colorless foam, 90%; ^1H NMR (400 MHz, CDCl_3): δ 0.64 (t, $J = 7.5$ Hz, 3H), 0.87 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 3H), 1.29 (s, 9H), 2.25–2.36 (m, 2H), 2.46–2.60 (m, 2H), 3.22 (dd, $J = 6.6, 16$ Hz, 1H), 3.50 (dd, $J = 3.3, 16$ Hz, 1H), 3.56–3.68 (m, 4H), 4.08 (q, $J = 7.1$ Hz, 1H), 4.17 (t, $J = 7.0$ Hz, 2H), 4.19 (q, $J = 7.1$ Hz, 1H), 4.59 (d, $J = 15$ Hz, 1H), 4.67 (d, $J = 15$ Hz, 1H), 5.26 (dd, $J = 3.3, 6.3$ Hz, 1H), **6.47 and 6.63** ($2 \times$ s, **1H, 10.5:89.5**), 7.01–7.15 (m, 4H), 7.41–7.47 (m, 2H), 7.74–7.79 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 13.3, 13.7, 22.1, 22.6, 28.7, 29.2, 30.4, 31.0, 31.7, 31.9, 35.0, 44.6, 46.4, 53.6, 54.1, 62.8, 72.4, 72.5, 84.8, 98.2, 100.0, 102.1, 105.3, 114.8, 126.95, 126.02, 126.2, 126.87, 126.90, 127.1, 128.5, 131.0, 131.1, 132.0, 136.2, 152.7, 156.3, 157.9, 159.2, 163.7, 167.5, 168.9; IR (Nujol) 2223, 1759, 1748, 1660, 1617, 1353, 1165 cm^{-1} ; MS (APCI) m/z 746 ($[\text{M}+\text{H}]^+$).

N-4-*cyclo*-Hexylbenzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32j**: colorless foam, 88%; ^1H NMR (400 MHz, CDCl_3): δ 0.65 (t, $J = 7.4$ Hz, 3H), 0.86 (br. s, 3H), 1.13 (t, $J = 7.1$ Hz, 3H), 1.24 (br. s, 3H), 1.25–1.47 (m, 5H), 1.55–1.90 (m, 5H), 2.24–2.36 (m, 2H), 2.44–2.61 (m, 3H), 3.23 (dd, $J = 6.4, 16$ Hz, 1H), 3.50 (dd, $J = 3.1, 16$ Hz, 1H), 3.56–3.68 (m, 4H), 3.90–4.01 (m, 1H), 4.05–4.24 (m, 3H), 4.61 (d, $J = 15$ Hz, 1H), 4.65 (d, $J = 15$ Hz, 1H), 5.27 (dd, $J = 3.1, 6.4$ Hz, 1H), **6.47 and 6.65** ($2 \times$ s, **1H, 10:90**), 6.99–7.07 (m, 1H), 7.09–7.18 (m, 3H), 7.23–7.29

(m, 2 H), 7.72–7.78 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 13.3, 13.7, 22.1, 22.6, 25.9, 26.6, 26.7, 28.1, 28.9, 29.2, 30.4, 31.9, 34.99, 34.01, 44.5, 44.6, 46.4, 53.6, 54.1, 62.7, 72.4, 72.5, 84.7, 98.3, 102.0, 105.3, 114.8, 126.2, 126.86, 126.88, 127.37, 127.42, 127.51, 128.53, 131.1, 132.0, 136.5, 152.7, 153.1, 158.02, 159.2, 167.4, 168.8; IR (Nujol) 2222, 1758, 1747, 1659, 1615, 1241, 1161, 1092, 1060, 750 cm^{-1} ; MS (APCI) m/z 772 ($[\text{M}+\text{H}]^+$).

N-4-Biphenylsulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32k**: colorless foam, 89%; ^1H NMR (400 MHz, CDCl_3): δ 0.70 (t, $J = 7.4$ Hz, 3H), 0.85 (br. s, 3H), 1.02 (t, $J = 7.1$ Hz, 3H), 1.21 (br. s, 3H), 2.16–2.55 (m, 4H), 3.35 (dd, $J = 6.4$, 16 Hz, 1H), 3.50 (dd, $J = 2.8$, 16 Hz, 1H), 3.55–3.70 (m, 4H), 3.70–3.90 (m, 2H), 3.93–4.16 (m, 2H), 4.68 (d, $J = 16$ Hz, 1H), 4.76 (d, $J = 16$ Hz, 1H), 5.37 (dd, $J = 2.8$, 6.4 Hz, 1H), **6.46 and 6.71** ($2 \times$ s, **1H, 8:92**), 7.02–7.10 (m, 1H), 7.10–7.20 (m, 3H), 7.36–7.50 (m, 3H), 7.54–7.59 (m, 2H), 7.63–7.68 (m, 2H), 7.89–7.96 (m, 2H); IR (Nujol) 2222, 1757, 1746, 1658, 1614, 1240, 1164, 1094, 1060, 762 cm^{-1} ; MS (APCI) m/z 766 ($[\text{M}+\text{H}]^+$).

N-(2-Naphthalene)sulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32l**: pale yellow foam, 91%; ^1H NMR (400 MHz, CDCl_3): δ 0.60 (t, $J = 7.5$ Hz, 3H), 0.86 (s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H), 1.23 (s, 3H), 2.18–2.36 (m, 2H), 2.52 (t, $J = 7.0$ Hz, 2H), 3.24 (dd, $J = 6.4$, 16 Hz, 1H), 3.53 (dd, $J = 2.9$, 16 Hz, 1H), 3.60–3.70 (m, 4H), 3.83–3.95 (m, 1H), 3.96–4.08 (m, 1H), 4.11–4.22 (m, 2H), 4.71 (br. s, 2H), 5.36 (dd, $J = 3.1$, 6.4 Hz, 1H), **6.44 and 6.60** ($2 \times$ s, **1H, 9:91**), 7.00–7.20 (m, 4H), 7.55–7.65 (m, 2H), 7.78–7.92 (m, 3H), 7.94–8.00 (m, 1H), 8.46 (br., 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.1, 13.6, 22.1, 22.6, 28.6, 29.2, 30.4, 32.0, 44.6, 46.4, 54.1, 62.7, 72.4, 72.5, 84.8, 98.2, 102.1, 105.3, 114.8, 122.6, 126.1, 126.9, 127.3, 127.7, 128.6, 1288, 129.3, 129.4, 130.9, 131.8, 132.1, 134.8, 136.1, 152.7, 157.9, 159.1, 167.4, 168.7; IR (Nujol) 2223, 1747, 1659, 1616, $1350, 1161\text{ cm}^{-1}$; MS (APCI) m/z 740 ($[\text{M}+\text{H}]^+$).

N-(1-Naphthalene)sulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32m**: pale yellow foam, 91%; ^1H NMR (400 MHz, CDCl_3): δ 0.59 (t, $J = 7.4$ Hz, 3H), 0.86 (s, 3H), 1.13 (t, $J = 7.1$ Hz, 3H), 1.23 (s, 3H), 2.24–2.35 (br. q, $J = 7.6$ Hz, 2H), 2.49–2.57 (m, 2H), 3.19 (dd, $J = 6.4$, 17 Hz, 1H), 3.44–3.74 (m, 5H), 3.93–4.23 (m, 4H), 4.54 (d, $J = 16$ Hz, 1H), 4.87 (d, $J = 16$ Hz, 1H), 5.42 (dd, $J = 2.4$, 6.4 Hz, 1H), **6.49 and 6.63** ($2 \times$ s, **1H, 12.5:87.5**), 6.97–7.03 (m, 1H), 7.07–7.16 (m, 3H), 7.50–7.59 (m, 2H), 7.61–7.69 (m, 1H), 7.86–7.92 (m, 1H), 8.03 (br. d, $J = 8.2$ Hz, 1H), 8.36 (dd,

$J = 1.3, 7.5$ Hz, 1H), 8.59 (br. d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.1, 13.3, 13.6, 22.1, 22.6, 28.8, 29.3, 30.4, 31.7, 44.1, 46.4, 53.5, 62.5, 62.8, 72.4, 72.5, 84.8, 85.1, 98.3, 102.1, 105.3, 114.8, 124.1, 124.6, 126.1, 126.6, 126.77, 126.81, 128.3, 128.4, 128.7, 128.9, 130.4, 130.56, 130.62, 131.4, 134.1, 134.4, 134.5, 152.6, 157.9, 159.2, 167.5, 168.8; IR (Nujol) 2222, 1747, 1659, 1241, 1160, 1140, 1060, 759 cm^{-1} ; MS (APCI) m/z 740 ($[\text{M}+\text{H}]^+$).

N-(Indan-5-yl)sulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32n**: colorless foam, 90%; ^1H NMR (300 MHz, CDCl_3): δ 0.63 (t, $J = 7.4$ Hz, 3H), 0.87 (s, 3H), 1.15 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 3H), 2.08 (m, 2H), 2.31 (m, 2H), 2.53 (m, 2H), 2.90 (m, 4H), 3.20 (dd, $J = 16, 62\text{Hz}$, 1H), 3.49 (dd, $J = 16, 3.1$ Hz, 1H), 3.56–3.69 (m, 4H), 3.95–4.24 (m, 4H), 4.60 (d, $J = 16$ Hz, 1H), 4.66 (d, $J = 16$ Hz, 1H), 5.24 (dd, $J = 6.4, 3.3$ Hz, 1H), **6.49 and 6.63** ($2 \times$ s, **1H, 13:87**), 7.01–7.07 (m, 1H), 7.09–7.18 (m, 3H), 7.23–7.29 (m, 1H), 7.60–7.67 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 13.7, 14.2, 21.0, 22.1, 22.6, 25.3, 28.6, 29.3, 30.4, 31.9, 32.6, 32.8, 44.6, 46.4, 54.1, 60.4, 62.7, 72.4, 72.5, 84.8, 98.3, 102.2, 105.3, 114.7, 123.2, 124.7, 125.6, 126.2, 126.8, 126.9, 128.5, 131.1, 132.1, 137.0, 145.3, 149.8, 152.7, 157.9, 159.1, 167.48, 168.9; IR (Nujol) 2222, 1746, 1660, 1461, 1376, 1148 cm^{-1} ; MS (APCI) m/z 730 ($[\text{M}+\text{H}]^+$).

N-Benzylsulfonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ester **32o**: pale yellow foam, 94%; ^1H NMR (400 MHz, CDCl_3): δ 0.62 (t, $J = 7.4$ Hz, 3H), 0.86 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 3H), 2.28–2.38 (m, 2H), 2.49–2.56 (m, 2H), 3.12–3.24 (m, 1H), 3.51 (dd, $J = 3.0, 16$ Hz, 1H), 3.56–3.68 (m, 4H), 3.87–4.21 (m, 4H), 4.26 (d, $J = 14$ Hz, 1H), 4.32 (d, $J = 14$ Hz, 1H), 4.44 (d, $J = 15$ Hz, 1H), 4.56 (d, $J = 15$ Hz, 1H), 5.04 (dd, $J = 3.0, 6.4$ Hz, 1H), **6.54 and 6.61** ($2 \times$ s, **1H, 27.5:72.5**), 6.95–7.02 (m, 1H), 7.15–7.20 (m, 3H), 7.27–7.40 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.1, 13.4, 13.7, 22.1, 22.6, 22.6, 28.6, 28.8, 29.1, 29.2, 30.4, 31.3, 31.6, 45.1, 45.3, 46.5, 54.4, 54.7, 58.3, 58.4, 62.6, 62.8, 72.4, 72.5, 85.0, 85.1, 97.9, 98.3, 102.1, 102.3, 105.26, 105.31, 114.7, 125.9, 126.0, 126.8, 126.9, 127.02, 127.06, 128.65, 128.69, 128.8, 130.75, 130.8, 131.0, 131.1, 131.9, 132.2, 152.8, 157.5, 157.7, 159.1, 167.5, 169.5; IR (Nujol) 2223, 1751, 1659, 1617, 1244, 1151, 1061, 754 cm^{-1} ; MS (APCI) m/z 704 ($[\text{M}+\text{H}]^+$).

Synthesis of T-2513 (5)

Diester (*R*)-**31k**: To a solution of **63a** (34.1 g, 89.6 mmol) and (*R*)-**33j** (42.3 g, 107.6

mmol) in DMF (350 mL) was added K₂CO₃ (8.7 g, 62.7 mmol) at room temperature under an argon atmosphere. The mixture was stirred for 45 minutes at 60°C, and then cooled in an ice bath. To it were added EtOAc (200 mL), saturated aqueous NaHCO₃ (300 mL), and water (500 mL). The resulting mixture was extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with water (2 × 1 L) and saturated aqueous NaCl solution (1 L), dried over Na₂SO₄, treated with activated charcoal, filtered through Celite, and then evaporated under reduced pressure to give 662h (quant.) of diester (*R*)-**31k** as a pale yellow foam: (mixture of diastereo isomers) ¹H NMR (400 MHz, CDCl₃): δ 0.89 and 0.90 (2 × s, 3H), 1.10 and 1.15 (2 × t, *J* = 7.1 Hz, 3H), 1.33 and 1.35 (2 × s, 3H), 2.45–2.60 (m, 2H), 3.28, 3.33, and 3.39 (d, *J* = 4.6 Hz, dd, *J* = 6.2, 16 Hz, dd, *J* = 3.3, 16 Hz, total 2H), 3.61–3.76 (m, 4H), 3.95–4.22 (m, 4H), 4.58 and 4.68 (2 × d, *J* = 16 Hz, 1H), 4.72 and 4.75 (2 × d, *J* = 16 Hz, 1H), 5.22 and 5.28 (dd, *J* = 3.3, 6.2 Hz, t, *J* = 4.6 Hz, 1H), 6.01 and 6.04 (2 × s, 1H), 6.58 and 6.65 (2 × s, 1H), 7.02–7.20 (m, 4H), 7.37–7.51 (m, 3H), 7.54–7.60 (m, 2H), 7.62–7.68 (m, 2H), 7.85–7.93 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 13.7, 13.8, 22.06, 22.10, 22.69, 22.72, 29.1, 29.2, 30.47, 30.49, 31.7, 31.8, 44.4, 44.5, 46.5, 46.6, 53.6, 53.8, 62.9, 63.0, 71.96, 72.07, 72.5, 77.7, 98.9, 99.0, 104.2, 104.3, 105.3, 105.4, 113.4, 126.1, 126.9, 127.0, 127.2, 127.3, 127.5, 127.7, 127.8, 127.9, 128.5, 128.7, 128.8, 129.0, 130.3, 130.4, 131.2, 131.3, 137.1, 137.4, 139.0, 139.2, 145.5, 145.8, 153.55, 153.7, 154.0, 154.1, 158.0, 158.1, 164.86, 164.91, 168.7, 168.8; IR (Nujol) 2224, 1751, 1663, 1613 cm⁻¹; MS (APCI) *m/z* 738 ([M+H]⁺); HRMS (FAB, [M+H]⁺): calcd for C₄₀H₄₀N₃O₉S 738.2485, found 738.2469.

Optically pure intermediate (-)-**32k**: To a solution of diester (*R*)-**31k** (103.8 g, 140.7 mmol) in 1 L of 1:1 (v/v) *N,N*-dimethylacetamide/toluene was added NaH (60% oil suspension, 6.94 g, 173.5 mmol) at 6 °C under an argon atmosphere. The mixture was stirred for 1.5 hours at room temperature, and then iodoethane (217.0 g, 1.39 mol) was added dropwise to it over 5 minutes at 6 °C. Stirring was continued and the mixture was allowed to warm to room temperature. After 17 hours, it was poured into ice-cooled 2% aqueous citric acid (3 L). The resulting mixture was extracted with EtOAc (2 × 1 L). The combined organic extracts were washed with water (2 × 1 L) and saturated aqueous NaCl solution (1 L), dried over Na₂SO₄, treated with activated charcoal (15 g), filtered through Celite, and then evaporated under reduced pressure. To a solution of the residue in CHCl₃ (500 mL) was added silica gel (Fuji Silysia, BW-300, 32–53 μm, 200 g). The suspension was stirred for several minutes, and the silica gel was collected by filtration and washed with CHCl₃ (3 L). The

combined filtrate and washing was evaporated to dryness under reduced pressure. The residue was dissolved in hot acetone (140 mL), and diluted with *n*-hexane (120 mL). Separated crystals were collected by filtration, washed with 7:6 acetone/*n*-hexane (200 mL), and dried under reduced pressure to give 88.9 g (75%) of compound (-)-**32k** as colorless crystals: (single isomer) mp 121–135 °C; $[\alpha]_D^{26} = -43.3$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.70 (t, *J* = 7.4 Hz, 3H), 0.85 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 3H), 2.16–2.47 (m, 4H), 3.35 (dd, *J* = 6.4, 16 Hz, 1H), 3.50 (dd, *J* = 2.8, 16 Hz, 1H), 3.54–3.63 (m, 4H), 3.68–3.87 (m, 2H), 3.94–4.09 (m, 2H), 4.67 (d, *J* = 15 Hz, 1H), 4.77 (d, *J* = 15 Hz, 1H), 5.37 (dd, *J* = 2.8, 6.4 Hz, 1H), 6.71 (s, 1H), 7.03–7.10 (m, 1H), 7.12–7.20 (m, 3H), 7.36–7.49 (m, 3H), 7.54–7.59 (m, 2H), 7.63–7.68 (m, 2H), 7.90–7.95 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.5, 13.7, 22.1, 22.6, 29.0, 29.8, 30.4, 32.2, 44.4, 46.3, 53.7, 62.6, 72.3, 72.4, 84.4, 98.4, 101.5, 105.3, 114.8, 126.2, 126.8, 126.9, 127.4, 127.6, 127.8, 128.3, 128.7, 128.9, 131.0, 131.7, 137.8, 139.4, 145.2, 152.5, 158.6, 159.1, 167.2, 168.6; IR (Nujol) 2219, 1758, 1737, 1703, 1657, 1611, 1225, 1165, 1059 cm⁻¹; MS (APCI) *m/z* 766 ([M+H]⁺); elemental analysis calcd (%) for C₄₂H₄₃N₃O₉S•0.2H₂O: C 65.56, H 5.68, N 5.46, S 4.1; found: C 65.40, H 5.53, N 5.39, S 4.15. CHIRALPAK AD column (4.6 mm × 250 mm); 60:40 *n*-hexane/EtOH; 0.5 ml/min; 265 nm detector; (-)-**32k**, 35.8 min; (+)-**32k**, 18.6 min.

Acetamide (-)-**68**: A solution of compound (-)-**32k** (49.9 g, 59.3 mmol) in AcOH (400 mL) and Ac₂O (1 L) was hydrogenated in the presence of Raney Ni (Aldrich, active catalyst, 50% slurry in water, 100 g, prewashed with AcOH (100 mL)) under ambient H₂ pressure at 60 °C for 4.5 hours. The catalyst was collected by filtration, and washed with AcOH (200 mL) and CHCl₃ (1 L). The combined filtrate and washing was evaporated under reduced pressure. To a solution of the residual oil in CHCl₃ (300 mL) was added silica gel (100 g). The suspension was stirred for 30 minutes, and then the silica gel was collected by filtration and washed with CHCl₃ (2 L) and 100:1 CHCl₃/CH₃OH (2 L). The combined filtrate and washings were evaporated under reduced pressure to give 50.0 g (quant.) of acetamide (-)-**68** as a pale brown foam: $[\alpha]_D^{26} = -14.9$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.69 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H), 1.96 (s, 3H), 2.10–2.54 (m, 4H), 3.30 (dd, *J* = 6.4, 16 Hz, 1H), 3.41 (dd, *J* = 3.3, 16 Hz, 1H), 3.59 (s, 2H), 3.62 (s, 2H), 3.79–3.90 (m, 1H), 3.95–4.14 (m, 3H), 4.53 (dd, *J* = 5.1, 14 Hz, 1H), 4.60–4.70 (m, 1H), 4.62 (d, *J* = 16 Hz, 1H), 4.71 (d, *J* = 16 Hz, 1H), 5.25 (dd, *J* = 3.1, 6.3 Hz, 1H), 6.73 (s, 1H), 7.00–7.07 (m, 1H), 7.10–7.18 (m, 4H), 7.35–7.50 (m, 3H), 7.53–7.64

(m, 4H), 7.85 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.8, 13.7, 22.2, 22.6, 23.4, 29.3, 29.6, 30.4, 32.0, 37.1, 44.4, 45.5, 54.2, 62.2, 72.3, 72.4, 86.2, 99.9, 105.2, 125.9, 126.1, 126.9, 126.9, 127.3, 127.5, 127.8, 128.3, 128.8, 128.9, 130.9, 131.6, 137.9, 139.4, 145.4, 146.4, 147.9, 161.8, 168.5, 168.7, 169.6; IR (Nujol) 1751, 1656, 1595 cm^{-1} ; MS (ESI) m/z 812 ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for $\text{C}_{44}\text{H}_{49}\text{N}_3\text{O}_{10}\text{S}\cdot 0.3\text{CHCl}_3$: C 62.76, H 5.86, N 4.96, S 3.78; found: C 62.67, H 5.85, N 4.91, S 3.79.

Triester (-)-**69**: To a solution of acetamide (-)-**68** (80.0 g, 98.5 mmol) in a mixture of AcOH (240 mL) and Ac_2O (480 mL) was added pyridine (1.6 mL, 19.7 mmol) at room temperature under an argon atmosphere. To this mixture was added NaNO_2 (8.84 g, 128 mmol) at 7 °C, and then the cooling bath was removed. To the reaction mixture was added additional NaNO_2 (4.76 g, 69.0 mmol + 1.36 g, 19.7 mmol) at 1.5 hour intervals at room temperature. After completion of the addition of NaNO_2 , the mixture was stirred at room temperature for a further 0.5 hours, then diluted with EtOAc (480 mL), and heated at 60 °C for 1 hour. To this mixture were added water (700 mL) and EtOAc (250 mL). The organic phase was separated, washed with water (500 mL) and saturated aqueous NaCl solution (500 mL), dried over MgSO_4 , treated with activated charcoal, filtered through Celite, and then evaporated under reduced pressure. To a solution of the residual foam in methanol (480 mL) was added water (480 mL) in portions with stirring. The resulting precipitate was collected by filtration, and dried under reduced pressure to give 68.5 g (86%) of triester (-)-**69** as a pale yellow crystalline solid: mp 145–147 °C; $[\alpha]_D^{27} = -9.60$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 0.54 (t, $J = 7.3$ Hz, 3H), 0.88 (s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H), 1.30 (s, 3H), 2.08 (s, 3H), 2.23 (q, $J = 7.5$ Hz, 2H), 2.46 (t, $J = 7.0$ Hz, 2H), 3.20–3.35 (m, 2H), 3.57–3.70 (m, 4H), 3.90–4.20 (m, 4H), 4.63 (d, $J = 16$ Hz, 1H), 4.73 (d, $J = 16$ Hz, 1H), 5.12 (dd, $J = 3.6, 5.7$ Hz, 1H), 5.23 (d, $J = 11$ Hz, 1H), 5.26 (d, $J = 11$ Hz, 1H), 6.66 (s, 1H), 7.02–7.18 (m, 4H), 7.38–7.50 (m, 3H), 7.54–7.60 (m, 2H), 7.61–7.68 (m, 2H), 7.86–7.92 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.2, 13.6, 20.9, 22.1, 22.7, 28.3, 29.3, 30.4, 32.0, 44.5, 45.7, 54.4, 58.5, 62.3, 72.38, 72.43, 86.1, 98.7, 105.4, 123.4, 126.2, 127.0, 127.1, 127.3, 127.6, 127.8, 127.9, 128.4, 128.6, 129.0, 130.5, 131.6, 137.7, 139.3, 145.5, 148.3, 149.9, 161.1, 168.3, 168.6, 170.9; IR (Nujol) 1757, 1660, 1615, 1241 cm^{-1} ; MS (ESI) m/z 813, ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for $\text{C}_{44}\text{H}_{48}\text{N}_2\text{O}_{11}\text{S}\cdot\text{H}_2\text{O}$: C 63.64, H 6.11, N 3.51, S 3.83; found: C 63.78, H 5.93, N 3.27, S 3.73.

Tricyclic ketone (-)-**64k**: A solution of triester (-)-**69** (31.0 g, 38.2 mmol) in 80% aqueous TFA (310 mL) was heated at 80 °C for 45 minutes, and allowed to cool to room temperature. The solvent was removed by distillation under reduced pressure, and then water and CHCl₃ were added to the residue. The organic phase was separated and the aqueous phase was extracted with CHCl₃ (2 × 500 mL). The combined organic phases were washed with water (1 L) and saturated aqueous NaCl solution, dried over Na₂SO₄, treated with activated charcoal, filtered through Celite, and then evaporated under reduced pressure. To a solution of the residual foam in CHCl₃ (300 mL) was added silica gel (100 g). The suspension was stirred for 30 minutes, then the silica gel was collected by filtration and washed with CHCl₃ (1 L) and 100:1 CHCl₃/CH₃OH (1 L). The combined filtrate and washings were evaporated under reduced pressure to give 26.7 g (quant.) of tricyclic ketone (-)-**64k** as a pale yellow foam, which was used for the next step without further purification. To obtain an analytical sample, a small quantity of the foam was purified by column chromatography on silica gel (CHCl₃ then CHCl₃/EtOAc, 3:1) to give purified tricyclic ketone (-)-**64k** as colorless needles: mp 209–211 °C (dec.); $[\alpha]_D^{25} = -16.36$ (*c* 1.01, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.82 (t, *J* = 7.5 Hz, 3H), 1.80–2.05 (m, 2H), 2.73 (ddd, *J* = 5.0, 8.8, 20 Hz, 1H), 2.82 (ddd, *J* = 4.6, 8.7, 20 Hz, 1H), 3.17–3.28 (m, 2H), 4.05–4.25 (m, 2H), 4.52 (d, *J* = 15 Hz, 1H), 4.70 (d, *J* = 15 Hz, 1H), 5.00 (t, *J* = 5.1 Hz, 1H), 5.22 (d, *J* = 18 Hz, 1H), 5.49 (d, *J* = 18 Hz, 1H), 6.57 (s, 1H), 7.00–7.20 (m, 4H), 7.38–7.58 (m, 5H), 7.59–7.65 (m, 2H), 7.85–7.90 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.4, 14.2, 31.4, 31.7, 33.4, 42.0, 44.8, 53.9, 60.4, 66.8, 76.3, 98.8, 125.5, 125.9, 127.1, 127.2, 127.3, 127.7, 127.8, 128.5, 128.6, 129.1, 130.8, 131.5, 137.5, 139.2, 139.6, 144.6, 145.6, 157.2, 166.0, 169.9, 195.5; IR (Nujol) 1763, 1659 cm⁻¹; MS (APCI) *m/z* 639 ([M+H]⁺); elemental analysis calcd (%) for C₃₅H₃₀N₂O₈S•0.1H₂O: C 65.63, H 4.75, N 4.37, S 5.00; found: C 65.42, H 4.68, N 4.19, S 4.88.

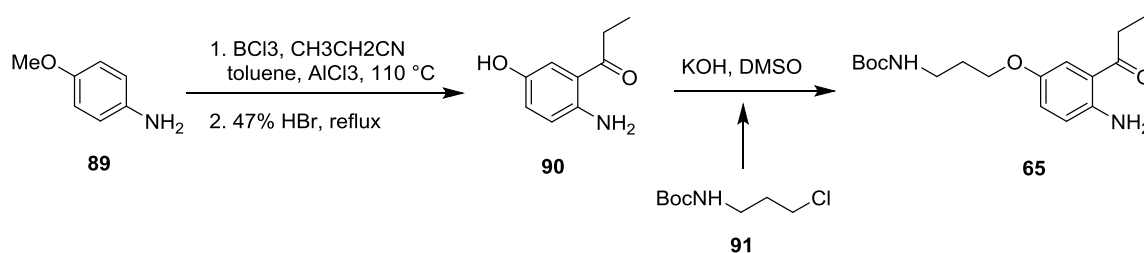
Camptothecin ester (-)-**66**: A solution of tricyclic ketone (-)-**64k** (24.4 g, 38.2 mmol) and amino ketone **65** (18.4 g, 57.2 mmol) in AcOH (300 mL) was stirred at 60 °C for 4 days under an argon atmosphere, and then allowed to cool to room temperature. The reaction mixture was added in portions to slurry of silica gel (400 g) in *n*-hexane (1 L) with stirring. The suspension was stirred for 1 hour, and then the silica gel was collected by filtration and washed successively with *n*-hexane (3 L) and *i*-Pr₂O (6 L) in order to remove AcOH. (-)-**15** was eluted from the residual silica gel cake with CHCl₃ (3 L) and 100:1 CHCl₃/CH₃OH (4 L), and the eluate was evaporated under reduced

pressure. The residual brown foam was dissolved in hot *i*-PrOH (400 mL), seeded with an authentic sample, and then allowed to cool to room temperature with stirring. After 2.5 hours, the resulting precipitate was collected by filtration, washed with *i*-PrOH (100 mL) and *i*-Pr₂O (180 mL), and dried under reduced pressure to give 25.0 g (71%) of camptothecin ester (-)-**66** as a brown crystalline solid: mp 212–214 °C (dec.); $[\alpha]_D^{25} = -136.72$ (*c* 1.02, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.86 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.6 Hz, 3H), 1.45 (s, 9H), 1.88–2.18 (m, 4H), 2.94–3.20(m, 2H), 3.34 (d, *J* = 4.8 Hz, 2H), 3.42 (q like, *J* = 6.4 Hz, 2H), 4.22 (t, *J* = 6.0 Hz, 2H), 4.57 (d, *J* = 15 Hz, 1H), 4.73–4.81 (br., 1H), 4.81 (d, *J* = 15 Hz, 1H), 4.90 (d, *J* = 19 Hz, 1H), 5.09 (d, *J* = 19 Hz, 1H), 5.20 (t, *J* = 4.8 Hz, 1H), 5.25 (d, *J* = 17 Hz, 1H), 5.51 (d, *J* = 17 Hz, 1H), 6.99 (s, 1H), 7.02–7.18(m, 4H), 7.22–7.29 (m, 2H), 7.30–7.42 (m, 6H), 7.49 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.88 (d like, *J* = 8.6 Hz, 2H), 8.19 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 7.5, 13.6, 23.1, 28.4, 29.7, 31.7, 32.0, 37.9, 44.6, 49.2, 53.6, 66.2, 66.9, 76.8, 79.4, 95.3, 102.5, 119.0, 122.7, 126.0, 126.8, 127.0, 127.1, 127.5, 127.7, 128.2, 128.8, 128.9, 130.6, 131.2, 132.1, 137.7, 139.2, 143.6, 145.2, 145.3, 145.4, 147.0, 149.3, 156.1, 157.2, 158.2, 166.5, 169.4; IR (Nujol) 3407, 1763, 1753, 1709, 1669, 1614, 1514, 1335, 1241, 1226, 1161, 1147 cm⁻¹; MS (ESI) *m/z*, 925 ([M+H]⁺); elemental analysis calcd (%) for C₅₂H₅₂N₄O₁₀S•0.3H₂O: C 67.13, H 5.74, N 6.13, S 3.42; found: C 66.91, H 5.69, N 6.00, S 3.44.

(20*S*)-10-(3-Aminopropoxy)-7-ethylcamptothecin (T-2513 (**5**)): To a suspension of camptothecin ester (-)-**66** (28.0 g, 30.3 mmol) in CH₃OH (800 mL)-water (170 mL) was added LiOH•H₂O (5.26 g, 125 mmol) at room temperature. The reaction mixture was stirred for 1 day, and then concentrated to 1/6 volume under reduced pressure. To the residue were added CHCl₃ (800 mL) and AcOH (170 mL) on an ice-water bath. The resulting mixture was stirred for 1 day and diluted with water. The organic phase was separated, and the aqueous phase was extracted with CHCl₃ (500 mL). The combined organic phases were washed with water (2 × 1 L) and saturated aqueous NaCl solution, dried over Na₂SO₄, treated with activated charcoal, filtered through Celite, and then evaporated under reduced pressure. To a solution of the residual foam in EtOAc (300 mL) was added 1.22 M HCl in EtOAc (300 mL) at 5 °C. The mixture was stirred and allowed to warm to room temperature. After 7 hours, separated crystals were collected by filtration, washed with EtOAc (300 mL), and dried under reduced pressure. The obtained dark yellow crystalline solid was dissolved in hot water (30 mL)/*i*-PrOH (600 mL), seeded with an authentic sample, and then allowed to cool to room temperature with stirring. The resulting precipitate was

collected by filtration, washed with 20:1 *i*-PrOH/water (130 mL), and dried under reduced pressure at 60 °C. The orange crystalline solid thus obtained was dissolved in hot water (20 mL)/*i*-PrOH (180 mL), seeded with an authentic sample, and then allowed to cool to room temperature. The resulting precipitate was collected by filtration, washed with 20:1 *i*-PrOH/water (120 mL), and dried under reduced pressure at 60 °C to give 9.79 g (64%) of T-2513 (**5**) as a yellow crystalline solid: mp 245–249 °C (dec.); $[\alpha]_D^{27} = +9.8$ (*c* 1.0, H₂O); ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.5 Hz, 3H), 1.80–1.94 (m, 2H), 2.10–2.20 (m, 2H), 3.04 (br. t *J* = 7.2 Hz, 2H), 3.19 (br. q, *J* = 7.4 Hz, 2H), 4.32 (t like, 2H), 5.25 (s, 2H), 5.43 (s, 2H), 6.51 (s, 1H), 7.26 (s, 1H), 7.46–7.53 (m, 2H), 8.06 (d, *J* = 8.7 Hz, 1H), 8.09–8.30 (br., 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 7.8, 13.5, 22.2, 26.7, 30.3, 36.2, 49.5, 65.25, 65.33, 72.4, 96.0, 103.0, 118.3, 122.3, 127.8, 128.3, 131.4, 143.8, 144.4, 146.2, 149.6, 150.0, 156.8, 157.3, 172.5; IR (Nujol) 3567, 3362, 3286, 1741, 1654, 1589, 1513, 1242, 1165, 1035, 826, 722 cm⁻¹; MS (APCI) *m/z* 450, ([M+H]⁺); elemental analysis calcd (%) for C₂₅H₂₇N₃O₅•HCl•H₂O: C 59.58, H 6.00, N 8.34, Cl 7.03; found: C 59.45, H 6.05, N 8.26, Cl 6.83. CHIRALPAK IC-3 column (4.6 mm × 150 mm); 20:80:0.5 THF/EtOH/*n*-BuNH₂; 0.5 ml/min; 266 nm detector; (*R*)-**5**, 7.4 min; (*S*)-**5**, 9.2 min.

Synthesis of amino ketone **65**



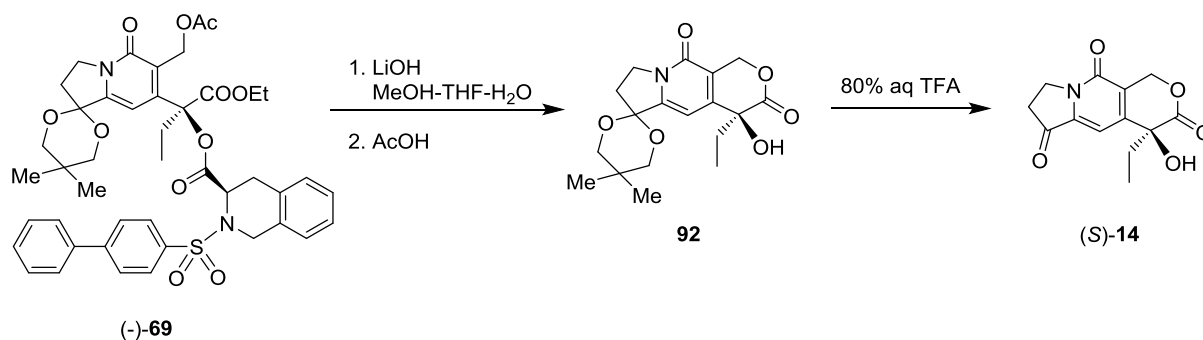
Scheme S4. Synthesis of amino ketone **65**.

Compound **90**^[54]: BCl₃ (1.0 M in CH₂Cl₂, 800 mL, 800 mmol) was added to toluene (1.5 L) keeping the temperature below 10 °C under an argon atmosphere. To the solution was added propionitrile (81.8 g, 1.49 mol) dropwise over 45 minutes at the same temperature. The mixture was stirred for 15 minutes, and then a solution of *para*-anisidine (**89**) (89.5 g, 727 mmol) in toluene (800 mL) was added dropwise to it over 1 hour at the same temperature, and then AlCl₃ (107.9 g, 809 mmol) was added to the resulting mixture. The whole mixture was heated at 110 °C for 17 hours, and then

allowed to cool to 55 °C. To the mixture was added 47% aqueous HBr (1.9 L) dropwise. The toluene phase was removed by decantation, and then the aqueous phase was heated to reflux for 22 hours. The mixture was cooled to room temperature, diluted with water (1.5 L), and then adjusted to pH 3.5 by the addition of aqueous NaOH. The resulting precipitate was collected by filtration, washed with water (800 mL), air-dried, and dried under reduced pressure to give 60.0 g (50%) of compound **90** as yellow crystals: mp 147–148 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.05 (t, *J* = 7.2 Hz, 3H), 2.87 (q, *J* = 7.2 Hz, 2H), 6.62 (s, 2H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 2.8, 9.0 Hz, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 8.66 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 8.8, 31.7, 114.8, 116.6, 118.2, 123.7, 144.5, 146.3, 202.0; IR (Nujol) 3375, 3293, 1670 cm⁻¹; MS (APCI) *m/z* 166 ([M+H]⁺); elemental analysis calcd (%) for C₉H₁₁NO₂: C 65.43, H 6.71, N 8.48; found: C 65.39, H 6.63, N 8.54.

Amino ketone **65**: To a solution of compound **90** (50.0 g, 303 mmol) in DMSO (500 mL) was added powdered KOH (26.7 g, 457 mmol) at 24 °C under an argon atmosphere. The mixture was stirred for 34 minutes at 24–34 °C, and then a solution of 3-(*t*-butoxycarbonylamino)propyl chloride (**91**)^[55] (98.2 g, 507 mmol) in DMSO (200 mL) was added dropwise to it over 7 minutes at 32–41 °C. The whole mixture was stirred for 2.5 hours at room temperature, and then poured into ice-water (6 L). The mixture was acidified with 10% aqueous citric acid solution (300 mL) to pH 3, and then extracted with EtOAc (4 L + 2 L). The combined organic extracts were washed with water (3 × 4 L) and saturated aqueous NaCl solution (1.4 L), dried over Na₂SO₄, treated with activated charcoal (40 g), filtered through Celite, and then evaporated under reduced pressure. The resulting yellow solid was recrystallized from EtOH (250 mL) to give 79.7 g (82%) of amino ketone **65** as yellow crystals: mp 121.5–124 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 1.96 (quintet, *J* = 6.3 Hz, 2H), 2.95 (q, *J* = 7.2 Hz, 2H), 3.33 (q, *J* = 6.2 Hz, 2H), 3.96 (t, *J* = 5.9 Hz, 2H), 4.8 (br, 1H), 5.97 (br, 2H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.95 (dd, *J* = 2.8, 9.0 Hz, 1H), 7.24 (d, *J* = 3.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 8.6, 28.4, 29.7, 32.4, 38.0, 67.0, 79.2, 115.2, 117.8, 118.6, 123.3, 145.1, 149.1, 156.0, 202.8; IR (Nujol) 3450, 3400, 3340, 2950, 2930, 2850, 1700, 1650, 1580 cm⁻¹; MS (ESI) *m/z* 345 ([M+Na]⁺); elemental analysis calcd (%) for C₁₇H₂₆N₂O₄: C 63.33, H 8.13, N 8.69; found: C 63.17, H 8.18, N 8.58.

Synthesis of tricyclic ketone (S)-14



Scheme S5. Synthesis of amino ketone (S)-14.

Lactone **92**: To a solution of (-)-**69** (5.80 g, 7.14 mmol) in methanol (116 mL)-THF (29 mL)-water (29 mL) was added LiOH•H₂O (1.60 g, 38.5 mmol) at room temperature. The reaction mixture was stirred for 3 hours at room temperature, and then concentrated to 1/6 volume under reduced pressure. To the residue were added CHCl₃ (116 mL) and AcOH (23 mL) at room temperature. The resulting mixture was stirred for 15.5 hours and diluted with water (100 mL). The organic phase was separated, and the aqueous phase was extracted with CHCl₃ (100 mL). The combined organic phases were washed with water and saturated aqueous NaCl solution, dried over Na₂SO₄, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Fuji Silysia, BW-300, 32–53 μm, 300 g, *n*-hexane/EtOAc, 1:1 then CHCl₃/CH₃OH, 50:1) to give 2.76 g (quant.) of lactone **92** as pale yellow crystals: mp 202–205 °C; [α]_D²⁶ = +85.57 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.88 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H), 1.29 (s, 3H), 1.73–1.90 (m, 2H), 2.50–2.57 (m, 2H), 3.60–3.72 (m, 4H), 3.78 (br, 1H), 4.07–4.21 (m, 2H), 5.17 (d, *J* = 16 Hz, 1H), 5.59 (d, *J* = 16 Hz, 1H), 6.81 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 7.76, 22.1, 22.64, 29.53, 30.41, 31.37, 45.49, 66.28, 72.5, 72.52, 72.63, 97.6, 105.26, 118.53, 149.58, 150.16, 157.41, 173.79; IR (Nujol) 3336, 1743, 1661, 1591, 1462, 1324, 1277, 1138, 1063 cm⁻¹; MS (APCI) *m/z* 350 ([M+H]⁺); elemental analysis calcd (%) for C₁₈H₂₃NO₆•0.2H₂O: C 61.25, H 6.68, N 3.97; found: C 61.06, H 6.49, N 3.87.

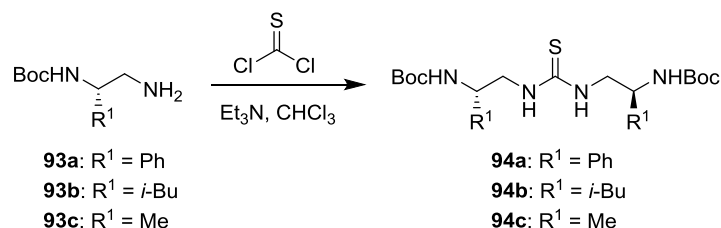
Tricyclic ketone (S)-**14**: A solution of lactone **92** (2.49 g, 7.14 mmol) in 80% aqueous TFA (37.5 mL) was stirred at room temperature for 2 hours, and then evaporated under

reduced pressure. The residue was purified by column chromatography on silica gel (Fuji Silysia, BW-300, 32–53 μm , 125 g, CHCl_3 then $\text{CHCl}_3/\text{CH}_3\text{OH}$, 50:1) to give 1.52 g (81%) of tricyclic ketone (*S*)-**14** as pale yellow crystals: mp 174–176 $^\circ\text{C}$ (lit.²⁷ mp 177.1–178.3 $^\circ\text{C}$); $[\alpha]_{\text{D}}^{26} = +116.14$ (c 1.0, CHCl_3); (lit.²⁷ $[\alpha]_{\text{D}}^{25} = +119.57$ (c 1.0, CHCl_3)); ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.73–1.88 (m, 2H), 2.92–2.99 (m, 2H), 3.68 (s, 1H), 4.27–4.41 (m, 2H), 5.24 (d, $J = 17$ Hz, 1H), 5.67 (d, $J = 17$ Hz, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.6, 31.7, 33.7, 42.2, 66.2, 72.3, 100.7, 124.5, 139.8, 149.3, 157.7, 173.2, 196.0; IR (Nujol) 3421, 2924, 1740, 1654, 1606, 1456, 1153 cm^{-1} ; MS (APCI) m/z 264 ($[\text{M}+\text{H}]^+$); elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{13}\text{NO}_5 \cdot 0.1\text{H}_2\text{O}$: C 58.91, H 5.02, N 5.28; found: C 58.74, H 4.81, N 5.28.

第3章の実験

Synthesis of guanidine-urea bifunctional organocatalysts 62d–62t

General procedure for synthesis of thioureas 94a–94c



Scheme S6. Synthesis of thioureas **94a–94c**.

To a solution of amine (**93a**,^[56] **93b**,^[56] or **93c**^[57]) (7 mmol) and Et₃N (7 mmol) in CHCl₃ (20 mL) was added a solution of thiophosgene (3.5 mmol) in CHCl₃ (10 mL) at room temperature dropwise over 10 minutes under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 hours, and poured into water (30 mL). The organic layer was separated, and the aqueous layer was extracted with CHCl₃ (30 mL). The combined organic extracts were washed with water (30 mL), dried over Na₂SO₄, filtered, and then evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give thiourea **94a–94c**.

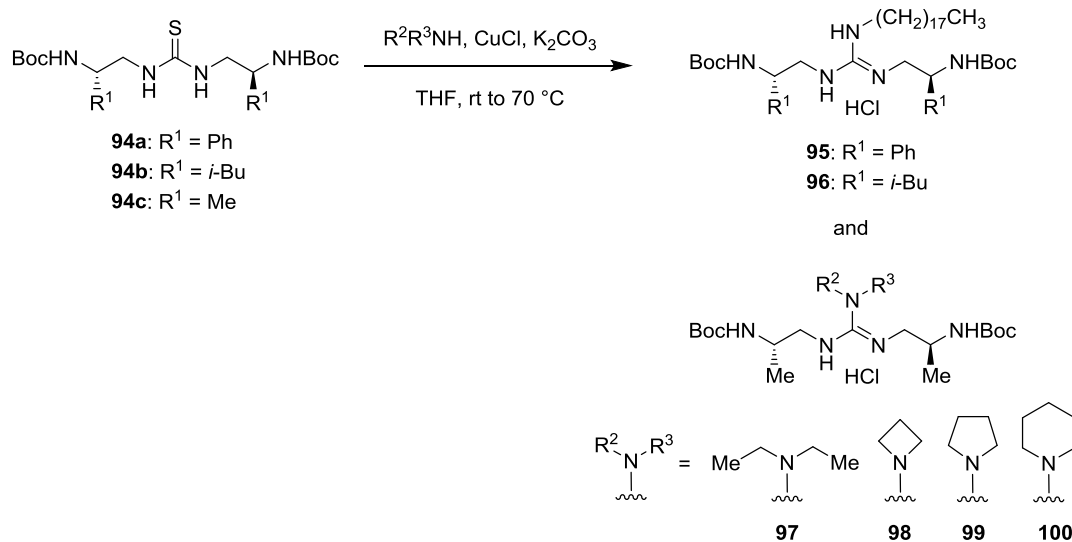
Thiourea **94a**: 74% yield; mp 187–189 °C; [α]_D²⁶ = +8.5 (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CD₃OD): δ 1.27 and 1.41 (br and s, 18H), 3.67 (br, 2H), 3.81 (br, 2H), 4.84 (overlapped with H₂O, 2H), 7.21–7.28 (m, 2H), 7.29–7.37 (m, 8H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 28.2, 48.8, 54.1, 77.8, 126.1, 126.8, 128.1, 142.0, 155.1, 183.2; IR (ATR) 3295, 1688, 1674, 1549, 1505, 1348, 1157, 1049, 1027 cm⁻¹; HRMS (ESI, [M+Na]⁺): calcd for C₂₇H₃₈N₄O₄SNa 537.2511, found 537.2558.

Thiourea **94b**: 39% yield; [α]_D²⁷ = -21.2 (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.91 (d, *J* = 6.7 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 6H), 1.18–1.40 (m, 4H), 1.44 (s, 18H), 1.60–1.77 (m, 2H), 3.15–4.03 (br, 6H); ¹³C NMR (100 MHz, CD₃OD): δ 21.9, 23.0, 24.2, 28.2, 41.4, 48.1, 77.4, 155.4, 182.8; IR (ATR) 3298, 1674, 1512, 1365, 1247, 1162 cm⁻¹; HRMS (ESI, [M+Na]⁺): calcd for C₂₃H₄₆N₄O₄SNa 497.3137, found 497.3173.

Thiourea **94c**^[58]: for details of the analytical data of thiourea **94c**, see the reference 58.

Synthesis of guanidines **95–98** and **100**

Table S2. Synthesis of guanidines **95–98** and **100** from thioureas **94a–94c**.^[a]



Entry	Thiourea	R ² R ³ NH	Product	Yield (%)
1	94a	CH ₃ (CH ₂) ₁₇ NH ₂	95	44
2	94b	CH ₃ (CH ₂) ₁₇ NH ₂	96	37
3	94c	Et ₂ NH	97	53
4 ^[b]	94c	Azetidine·HCl	98	67
5	94c	Piperidine	100	46

[a] Reactions were performed with thiourea (1.0 equiv), R²R³NH (1.5 equiv), CuCl (1.6 equiv), and K₂CO₃ (3.4 equiv) in THF at room temperature to 70 °C for 21 hours. [b] K₂CO₃ (4.5 equiv) was used for neutralization of azetidines·HCl.

Guanidine **95**: A suspension of thiourea **94a** (285 mg, 0.554 mmol), octadecylamine (225 mg, 0.835 mmol), CuCl (92 mg, 0.88 mmol), and K₂CO₃ (257 mg, 1.86 mmol) in THF (15 mL) was stirred at room temperature for 1 hour and at 70°C for 20 hours under a nitrogen atmosphere, and then allowed to cool to room temperature. To the reaction mixture were added saturated aqueous NH₄Cl (20 mL) and CHCl₃ (50 mL). Stirring was continued for 2 hours. The organic layer was separated and the aqueous layer was extracted with CHCl₃ (3 × 20 mL). The combined organic extracts were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (45 g, CHCl₃ to CHCl₃/CH₃OH = 4/1) to give 190 mg

(44%) of guanidine **95**: $[\alpha]_{\text{D}}^{29} = +5.6$ (*c* 1.4, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.20–1.60 (m, 50H), 3.05 (t, *J* = 7.2 Hz, 2H), 3.43 (br, 4H), 4.7 (br, 2H), 7.22–7.45 (m, 10H); ¹³C NMR (100 MHz, CD₃OD): δ 14.6, 23.9, 28.3, 29.0, 30.62, 30.66, 30.88, 30.93, 33.2, 43.7, 56.7 (br), 80.8, 128.1, 128.8, 129.8, 141.9, 156.5, 158.3; IR (ATR) 3385, 1693, 1629, 1494, 1364, 1250, 1168, 1050, 1026 cm⁻¹; HRMS (ESI, [M+H]⁺): calcd for C₄₅H₇₆N₅O₄ 750.5897, found 750.5875.

Guanidines **96–98**, and **100** were obtained in a similar manner as **95**.

Guanidine **96**: 37% yield; $[\alpha]_{\text{D}}^{29} = -9.5$ (*c* 1.4, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.86–0.98 (m, 15H), 1.20–1.55 (m, 52H), 1.60–1.80 (m, 4H), 3.16 (d, *J* = 6.2 Hz, 4H), 3.2 (t, *J* = 7.2 Hz, 2H), 3.56–3.72 (m, 2H); ¹³C NMR (100 MHz, CD₃OD): δ 14.6, 22.0, 23.87, 13.88, 26.1, 28.1, 29.0, 29.9, 30.56, 30.62, 30.80, 30.83, 30.9, 33.2, 42.1, 43.2, 48.5, 50.0, 80.9, 156.3, 159.3; IR (ATR) 3193, 1678, 1622, 1520, 1467, 1365, 1247, 1165, 1047, 1021 cm⁻¹; HRMS (ESI, [M+H]⁺): calcd for C₄₁H₈₄N₅O₄ 710.6523, found 710.6557.

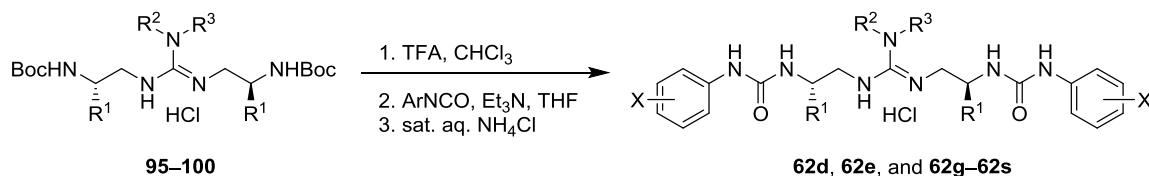
Guanidine **97**: 53% yield; $[\alpha]_{\text{D}}^{27} = -21.6$ (*c* 1.0, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.15 (d, *J* = 7.2 Hz, 6H), 1.16 (t, *J* = 7.7 Hz, 6H), 1.44 (s, 18H), 3.15 (dd, *J* = 7.7, 13 Hz, 2H), 3.21 (dd, *J* = 5.1, 13 Hz, 2H), 3.25–3.33 (m, 4H), 3.67–3.80 (m, 2H); ¹³C NMR (100 MHz, CD₃OD): δ 13.1, 18.9, 28.9, 44.2, 52.0, 80.3, 158.3, 160.8; IR (ATR) 3280, 1687, 1616, 1513, 1451, 1364, 1244, 1163 cm⁻¹; HRMS (ESI, [M+H]⁺): calcd for C₂₁H₄₄N₅O₄ 430.3393, found 430.3352.

Guanidine **98**: 67% yield; $[\alpha]_{\text{D}}^{27} = -10.1$ (*c* 2.0, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.15 (d, *J* = 7.2 Hz, 6H), 1.45 (s, 18H), 2.30–2.41 (m, 2H), 3.05–3.20 (m, 4H), 3.65–3.80 (m, 2H), 4.10–4.25 (m, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 16.9, 18.4, 28.9, 47.8, 50.4, 53.7, 80.4, 158.5 (br), 161.5; IR (ATR) 3286, 1686, 1612, 1518, 1450, 1364, 1246, 1163, 1054 cm⁻¹; HRMS (ESI, [M+H]⁺): calcd for C₂₀H₄₀N₅O₄ 414.3080, found 414.3080.

Guanidine **100**: 46% yield; $[\alpha]_{\text{D}}^{27} = -7.2$ (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.17 (d, *J* = 6.7 Hz, 6H), 1.44 (s, 18H), 1.69 (br, 6H), 3.17 (dd, *J* = 8.7, 13 Hz, 2H), 3.26–3.32 (2 H, overlapped with CH₃OH), 3.33–3.39 (m, 4H), 3.72–3.85 (m, 2H); ¹³C NMR (100 MHz, CD₃OD): δ 18.6, 25.0, 26.6, 28.9, 48.0, 50.4, 51.3, 80.6, 158.4, 160.9; IR (ATR) 3238, 1688, 1615, 1520, 1450, 1365, 1243, 1163, 1056 cm⁻¹; HRMS (ESI, [M+H]⁺): calcd for C₂₂H₄₃N₅O₄ 442.3393, found 442.3404.

Synthesis of guanidine-ureas **62d**, **62e**, and **62h–62t**

Table S3. Synthesis of compounds **62d**, **62e**, and **62h–62t** from guanidines **95–100**.^[a]



Entry	Guanidine	ArNCO	Product	Yield (%)
1	95	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62d	97
2	96	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62e	88
3	97	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62h	92
4	98	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62i	36
5	99 ^{40g}	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62j	40
6	100	3,5-di-CF ₃ -C ₆ H ₃ -NCO	62k	51
7	99	Ph-NCO	62l	40
8	99	3,5-di-F-C ₆ H ₃ -NCO	62m	29
8	99	2-CF ₃ -C ₆ H ₄ -NCO	62n	67
9	99	3-CF ₃ -C ₆ H ₄ -NCO	62o	47
10	99	4-CF ₃ -C ₆ H ₄ -NCO	62p	30
11	99	4-F-C ₆ H ₄ -NCO	62q	30
12	99	4-CF ₃ O-C ₆ H ₄ -NCO	62r	51
13	99	4-NO ₂ -C ₆ H ₄ -NCO	62s	9
14	99	4-MeO-C ₆ H ₄ -NCO	62t	46

[a] Reactions were performed according to the the procedure reported from our group.⁵⁷

Guanidine-ureas **62d**, **62e**, and **62h–62t** were synthesized according to the known procedure.^[40f, 58]

Guanidine-urea **62d**: $[\alpha]_D^{29} = +39.4$ (*c* 1.2, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.13–1.40 (m, 32H), 1.52–1.67 (m, 2H), 3.09–3.50 (m, 4H), 4.91–4.98 (m, 2H), 7.30–7.56 (m, 12H), 8.00 (s, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 14.4, 23.7, 27.9, 29.8, 30.3, 30.5, 30.56, 30.58, 30.66, 30.72, 30.75, 30.78, 33.1, 43.3,

48.5, 55.2, 115.9 (br), 119.1 (br), 124.8 (q, $J_{\text{C-F}} = 272.0$ Hz), 128.2, 129.5, 130.2, 133.3 (q, $J_{\text{C-F}} = 33.1$ Hz), 140.2, 143.0, 156.5, 157.5; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{53}\text{H}_{66}\text{F}_{12}\text{N}_7\text{O}_2$ 1060.5086, found 1060.5097.

Guanidine-urea **62e**: $[\alpha]_{\text{D}}^{27} = +1.7$ (c 1.5, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 0.89 (t, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 62$ Hz, 6H), 0.98 (d, $J = 6.7$ Hz, 6H), 1.10–1.37 (m, 30H), 1.40–1.58 (m, 4H), 1.58–1.71 (m, 2H), 1.72–1.85 (m, 2H), 3.21 (t, $J = 7.2$ Hz, 2H), 3.24–3.34 (m, 4H), 3.9 (br, 2H), 7.5 (s, 2H), 8.04 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.6, 22.1, 23.9, 26.2, 28.0, 29.9, 30.3, 30.59, 30.64, 30.66, 30.74, 30.80, 30.82, 30.87, 30.90, 33.2, 42.5, 43.2, 48.6, 115.9 (br), 119.2 (br), 124.9 (q, $J_{\text{C-F}} = 272.0$ Hz), 133.4 (q, $J_{\text{C-F}} = 33.1$ Hz), 143.3, 156.5, 158.2; IR (ATR) 3270, 3220, 3095, 1682, 1628, 1569, 1473, 1386, 1275, 1172, 1129 cm^{-1} ; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{49}\text{H}_{74}\text{F}_{12}\text{N}_7\text{O}_2$ 1020.5712, found 1020.5738.

Guanidine-urea **62h**: $[\alpha]_{\text{D}}^{27} = -42.4$ (c 1.3, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.18 (t, $J = 6.9$ Hz, 6H), 1.26 (d, $J = 7.2$ Hz, 6H), 3.26–3.34 (m, 2H), 3.35–3.49 (m, 6H), 4.04–4.15 (m, 2H), 7.47 (br, 2H), 8.02 (br, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 12.9, 18.7, 44.3, 47.3, 52.0, 115.8 (br), 119.1 (br), 124.8 (q, $J_{\text{C-F}} = 272$ Hz), 133.2 (q, $J_{\text{C-F}} = 32$ Hz), 143.2, 157.6, 160.7; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{29}\text{H}_{34}\text{F}_{12}\text{N}_7\text{O}_2$ 740.2582, found 740.2597.

Guanidine-urea **62i**: $[\alpha]_{\text{D}}^{29} = -22.2$ (c 1.3, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.27 (d, $J = 6.7$ Hz, 6H), 2.32–2.44 (m, 2H), 3.23–3.35 (m, 4H), 3.96–4.09 (m, 2H), 4.22–4.37 (m, 4H), 7.48 (s, 2H), 7.99 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 16.9, 18.4, 47.1, 50.0, 54.2, 115.9 (br), 119.2 (br), 124.9 (q, $J_{\text{C-F}} = 271.9$ Hz), 133.3 (q, $J_{\text{C-F}} = 33.3$ Hz), 143.3, 157.77, 157.82, 163.3, 163.7; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{28}\text{H}_{30}\text{F}_{12}\text{N}_7\text{O}_2$ 724.2269, found 724.2257.

Guanidine-urea **62j**: $[\alpha]_{\text{D}}^{29} = -34.6$ (c 1.1, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.26 (d, $J = 6.7$ Hz, 6H), 1.83–2.03 (m, 4H), 3.26–3.37 (m, 2H), 3.42 (dd, $J = 4.9, 13$ Hz, 2H), 3.43–3.58 (m, 4H), 3.98–4.14 (m, 2H), 7.49 (s, 2H), 8 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.6, 26.3, 47.3, 50.3, 51.5, 115.8 (br), 119.1 (br), 124.9 (q, $J_{\text{C-F}} = 271.7$ Hz), 133.2 (q, $J_{\text{C-F}} = 33.1$ Hz), 143.2, 157.6, 157.9; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{29}\text{H}_{32}\text{F}_{12}\text{N}_7\text{O}_2$ 738.2426, found 738.2401.

Guanidine-urea **62k**: $[\alpha]_{\text{D}}^{29} = -40.5$ (c 1.1, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ

1.25 (d, $J = 7.2$ Hz, 6H), 1.64 (m, 6H), 3.25–3.39 (m, 6H), 3.42 (dd, $J = 4.3, 13$ Hz, 2H), 4.03–4.15 (m, 2H), 7.48 (s, 2H), 8.01 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.8, 25.0, 26.7, 47.3, 50.5, 51.5, 115.8 (br), 119.2 (br), 125.0 (q, $J_{\text{C-F}} = 271.5$ Hz), 133.3 (q, $J_{\text{C-F}} = 33.3$ Hz), 143.3, 157.5, 161.0; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{30}\text{H}_{34}\text{F}_{12}\text{N}_7\text{O}_2$ 752.2582, found 752.2594.

Guanidine-urea **62l**: $[\alpha]_{\text{D}}^{27} = -50.6$ (c 1.2, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.22 (d, $J = 7.2$ Hz, 6H), 1.78–1.98 (m, 4H), 3.24 (dd, $J = 8.7, 13$ Hz, 2H), 3.42–3.54 (m, 4H), 3.43 (dd, $J = 4.4, 13$ Hz, 2H), 3.96–4.11 (m, 2H), 6.93–7.00 (m, 2H), 7.18–7.26 (m, 4H), 7.30–7.36 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.6, 26.3, 47.0, 50.3, 51.5, 120.3, 123.7, 129.9, 140.7, 157.8, 158.3; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{25}\text{H}_{36}\text{N}_7\text{O}_2$ 466.2931, found 466.2910.

Guanidine-urea **62m**: $[\alpha]_{\text{D}}^{27} = -51.3$ (c 1.2, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.24 (d, $J = 6.7$ Hz, 6H), 1.85–2.05 (m, 4H), 3.27 (dd, $J = 8.7, 14$ Hz, 2H), 3.41 (dd, $J = 4.6, 14$ Hz, 2H), 3.43–3.55 (m, 4H), 3.95–4.09 (m, 2H), 6.46–6.54 (m, 2H), 6.96–7.06 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.6, 26.4, 47.2, 50.3, 51.5, 97.9 (t, $J_{\text{C-F}} = 26$ Hz), 102.2 (d, $J_{\text{C-F}} = 30$ Hz), 143.7 (t, $J_{\text{C-F}} = 14$ Hz), 157.6, 157.8, 164.8 (dd, $J_{\text{C-F}} = 15, 244$ Hz); HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{25}\text{H}_{32}\text{F}_4\text{N}_7\text{O}_2$ 538.2554, found 538.2509.

Guanidine-urea **62n**: $[\alpha]_{\text{D}}^{27} = -10.8$ (c 1.2, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.24 (d, $J = 7.2$ Hz, 6H), 1.86–2.02 (m, 4H), 3.28 (dd, $J = 8.2, 13$ Hz, 2H), 3.39 (dd, $J = 4.6, 13$ Hz, 2H), 3.44–3.52 (m, 4H), 3.93–4.14 (m, 2H), 7.24 (t, $J = 7.7$ Hz, 2H), 7.54 (t, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 7.7$ Hz, 2H), 7.82 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.6, 26.3, 47.2, 50.3, 51.6, 122.9 (q, $J_{\text{C-F}} = 29$ Hz), 125.3, 125.5 (q, $J_{\text{C-F}} = 272$ Hz), 127.1 (q, $J_{\text{C-F}} = 5.8$ Hz), 127.3, 133.8, 137.6, 157.7, 158.3; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{27}\text{H}_{34}\text{F}_6\text{N}_7\text{O}_2$ 602.2678, found 602.2728.

Guanidine-urea **62o**: $[\alpha]_{\text{D}}^{27} = -40.6$ (c 1.2, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 1.24 (d, $J = 6.7$ Hz, 6H), 1.81–2.02 (m, 4H), 3.27 (dd, $J = 8.2, 13$ Hz, 2H), 3.40–3.55 (m, 4H), 3.43 (dd, $J = 4.4, 13$ Hz, 2H), 3.99–4.12 (m, 2H), 7.24 (brd, $J = 7.2$ Hz, 2H), 7.37–7.43 (m, 2H), 7.46 (brd, $J = 8.7$ Hz, 2H), 7.85 (br, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.5, 26.3, 47.1, 50.3, 51.6, 116.1 (q, $J_{\text{C-F}} = 3.9$ Hz), 119.7 (q, $J_{\text{C-F}} = 3.9$ Hz), 123.0, 125.7 (q, $J_{\text{C-F}} = 271$ Hz), 130.7, 132.0 (q, $J_{\text{C-F}} = 32$ Hz), 141.8, 157.9, 158.0; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{27}\text{H}_{34}\text{F}_6\text{N}_7\text{O}_2$ 602.2678, found 602.2723.

Guanidine-urea **62p**: $[\alpha]_D^{29} = -52.5$ (*c* 1.2, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.24 (d, *J* = 7.2 Hz, 6H), 1.80–2.02 (m, 4H), 3.29 (dd, *J* = 8.7, 14 Hz, 2H), 3.43 (dd, *J* = 4.4, 14 Hz, 2H), 3.43–3.55 (m, 4H), 3.98–4.11 (m, 2H), 7.47–7.56 (m, 8H); ¹³C NMR (100 MHz, CD₃OD): δ 18.6, 26.3, 47.2, 50.4, 51.4, 119.3, 125.0 (q, *J*_{C-F} = 32 Hz), 125.9 (q, *J*_{C-F} = 271 Hz), 127.1 (q, *J*_{C-F} = 3.9 Hz), 144.5, 157.76, 157.84; HRMS (ESI, [M+H]⁺): calcd for C₂₇H₃₄F₆N₇O₂ 602.2678, found 602.2650.

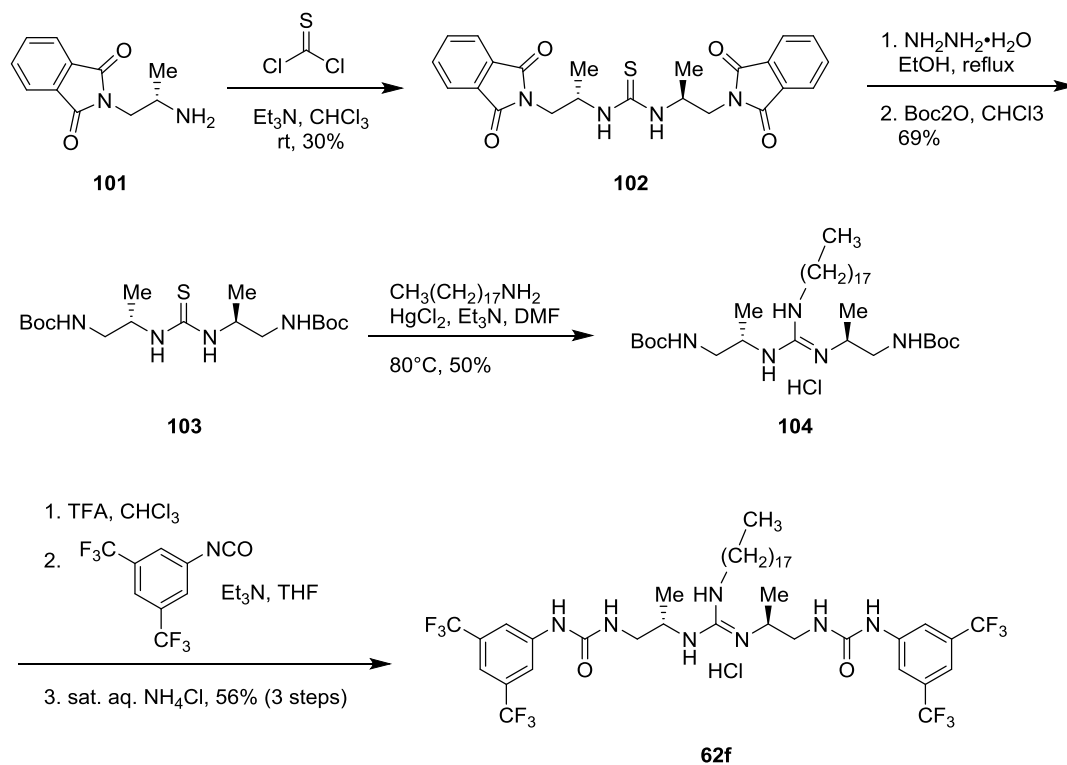
Guanidine-urea **62q**: $[\alpha]_D^{27} = -40.8$ (*c* 1.3, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.22 (d, *J* = 6.7 Hz, 6H), 1.80–2.00 (m, 4H), 3.24 (dd, *J* = 8.7, 13 Hz, 2H), 3.40–3.54 (m, 4H), 3.42 (dd, *J* = 4.4, 13 Hz, 2H), 3.94–4.09 (m, 2H), 6.92–7.01 (m, 4H), 7.29–7.35 (m, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 18.6, 26.3, 47.1, 50.3, 51.5, 116.3 (d, *J*_{C-F} = 22.3 Hz), 122.1 (d, *J*_{C-F} = 7.7 Hz), 136.8 (d, *J*_{C-F} = 2.3 Hz), 157.8, 158.4, 160 (d, *J*_{C-F} = 240 Hz); HRMS (ESI, [M+H]⁺): calcd for C₂₅H₃₄F₂N₇O₂ 502.2742, found 502.2724.

Guanidine-urea **62r**: $[\alpha]_D^{27} = -43.5$ (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.23 (d, *J* = 6.7 Hz, 6H), 1.80–2.03 (m, 4H), 3.27 (dd, *J* = 8.2, 13 Hz, 2H), 3.42 (dd, *J* = 4.6, 13 Hz, 2H), 3.42–3.54 (m, 4H), 3.97–4.09 (m, 2H), 7.14 (brd, *J* = 8.2 Hz, 4H), 7.38–7.45 (m, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 18.6, 26.3, 47.1, 50.3, 51.5, 121.1, 122.0 (q, *J*_{C-F} = 255 Hz), 122.8, 140.0, 145.3 (br), 157.8, 158.1; HRMS (ESI, [M+H]⁺): calcd for C₂₇H₃₄F₆N₇O₄ 634.2577, found 634.2576.

Guanidine-urea **62s**: $[\alpha]_D^{30} = -73.4$ (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.26 (d, *J* = 7.2 Hz, 6H), 1.86–2.07 (m, 4H), 3.33 (dd, *J* = 8.2, 13 Hz, 2H), 3.42 (dd, *J* = 4.6, 13 Hz, 2H), 3.46–3.56 (m, 4H), 3.96–4.11 (m, 2H), 7.50–7.60 (m, 4H), 8.07–8.14 (m, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 18.5, 26.4, 47.3, 50.4, 51.4, 118.6, 126.0, 143.3, 147.4, 157.3, 157.8; HRMS (ESI, [M+H]⁺): calcd for C₂₅H₃₄N₉O₆ 556.2632, found 556.2673.

Guanidine-urea **62t**: $[\alpha]_D^{27} = -56.9$ (*c* 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 1.22 (d, *J* = 6.7 Hz, 6H), 1.78–2.01 (m, 4H), 3.22 (dd, *J* = 8.5, 13 Hz, 2H), 3.41–3.55 (m, 4H), 3.43 (dd, *J* = 4.1, 13 Hz, 2H), 3.73 (s, 6H), 3.95–4.07 (m, 2H), 6.75–6.86 (m, 4H), 7.13–7.22 (m, 4H); ¹³C NMR (100 MHz, CD₃OD): δ 18.7, 26.3, 47.1, 50.3, 51.4, 55.9, 115.2, 122.8, 133.4, 157.3, 157.8, 158.7; HRMS (ESI, [M+H]⁺): calcd for C₂₇H₄₀N₇O₄ 526.3142, found 526.3174.

Synthesis of guanidine-ureas **62f**



Scheme S7. Synthesis of compound **62f**.

Thiourea **102**: To a solution of amine **101**^[59] (1.20 g, 5.88 mmol) and Et₃N (0.82 mL, 5.88 mmol) in CHCl₃ (15 mL) was added a solution of thiophosgene (0.23 mL, 3.0 mmol) in CHCl₃ (5 mL) dropwise over 5 minutes on ice-bath under a nitrogen atmosphere. The mixture was stirred at room temperature for 20 hours, and then poured into water (50 mL). The resulting mixture was extracted with CHCl₃ (2 × 30 mL). The organic extract was washed with water, dried over Na₂SO₄, filtered, and then evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (45 g, *n*-hexane/ethyl acetate = 7/3 to 1/3) to give 288 mg (30%) of **102** as a pale yellow solid: mp 94–95 °C; [α]_D²⁶ = +159.1 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.3 (d, *J* = 6.2 Hz, 6H), 3.8 (dd, *J* = 5.4, 14 Hz, 2H), 3.89 (dd, *J* = 6.7, 14 Hz, 2H), 4.49 (br, 2H), 6.39 (br, 2H), 7.67–7.74 (m, 4H), 7.78–7.84 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 18.4, 42.8, 49.4 (br), 123.4, 132.0, 134.1, 168.8, 180.6; MS (APCI): *m/z* 451 [M+H]⁺; HRMS (ESI, [M+Na]⁺): calcd for C₂₃H₂₂N₄O₄SNa 473.1259, found 473.1254.

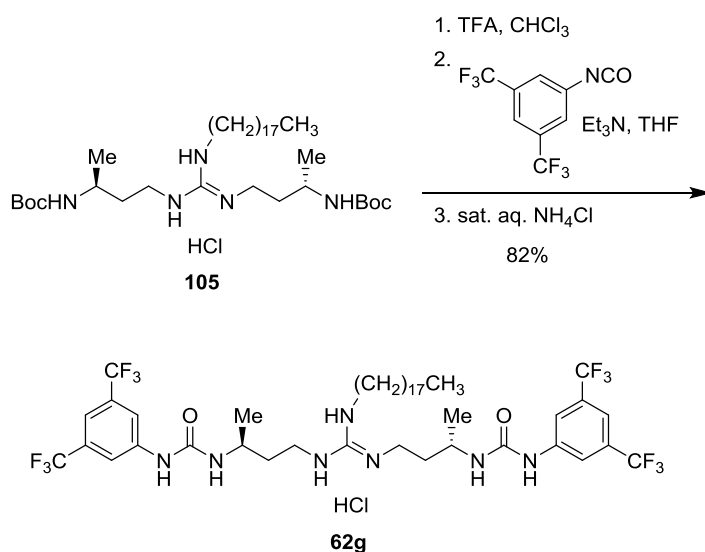
Thiourea **103**: To a solution of thiourea **102** (302 mg, 0.67 mmol) in ethanol (50 mL) was added hydrazine hydrate (0.2 mL, 4.0 mmol) at 50°C, and then the mixture was refluxed for 1 hour, and allowed to cool to room temperature. A separated precipitate was collected by filtration, and washed with ethanol. The filtrate and washings were combined, and evaporated under reduced pressure. To a solution of the residue in CHCl₃ (20 mL) was added a solution of Boc₂O (1.61 g, 7.38 mmol) in CHCl₃ (20 mL) at room temperature, and then the whole mixture was stirred at room temperature for 3 days. The mixture was diluted with water (30 mL), and it was extracted with CHCl₃ (2 × 30 mL). The organic extracts were washed with water, and then evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 g, *n*-hexane/ethyl acetate = 4/1 to 2/3) to give 180 mg (69%) of **103**: $[\alpha]_D^{26} = +6.3$ (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CD₃OD): δ 1.16 (d, *J* = 6.7 Hz, 6H), 1.43 (s, 18H), 2.90–3.27 (m, 4H), 4.35 (br, 2H); ¹³C NMR (100 MHz, CD₃OD): δ 18.2, 28.8, 46.5, 51.3 (br), 80.3, 159.0, 182.1; HRMS (ESI, [M+Na]⁺): calcd for C₁₇H₃₄N₄O₄SNa 413.2198, found 413.2217.

Guanidine **104**: A suspension of thiourea **103** (112 mg, 0.29 mmol), octadecylamine (117 mg, 0.43 mmol), HgCl₂ (113 mg, 0.42 mmol), and Et₃N (0.12 mL, 0.86 mmol) in DMF (10 mL) was stirred at 80 °C for 16 hours under a nitrogen atmosphere, and then allowed to cool to room temperature. The reaction mixture was diluted with CHCl₃, filtered through Celite, and then evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 g, *n*-hexane/ethyl acetate = 1/1, ethyl acetate, CHCl₃, and CHCl₃/CH₃OH = 3/1) to give a brown oil. It was purified by flash column chromatography on NH silica gel (30 g, CHCl₃ to CHCl₃/CH₃OH = 4/1) to give 94 mg (50%) of **104**: $[\alpha]_D^{30} = +11.0$ (*c* = 1.1, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.90 (t, *J* = 6.7 Hz, 3H), 1.22–1.43 (m, 30H), 1.27 (d, *J* = 6.7 Hz, 6H), 1.45 (s, 18H), 1.61–1.74 (m, 2H), 3.02 (dd, *J* = 6.4, 14 Hz, 2H), 3.17–3.27 (m, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 3.59–3.71 (m, 2H); ¹³C NMR (100 MHz, CD₃OD): δ 14.6, 18.2, 23.9, 28.1, 28.9, 29.9, 30.5, 30.6, 30.75, 30.82, 30.9, 33.2, 43.3, 47.1, 50.0, 81.0, 155.3, 159.7; HRMS (ESI, [M+H]⁺): calcd for C₃₅H₇₂N₅O₄ 626.5584, found 626.5574.

Guanidine-urea **62f**: According to the known procedure,^[58] guanidine **104** (91 mg, 0.14 mmol) was converted to 76 mg (56%) of compound **62f**: $[\alpha]_D^{30} = +39.2$ (*c* 1.2, CH₃OH); ¹H NMR (400 MHz, CD₃OD): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.14–1.32 (m, 30H), 1.35 (d, *J* = 6.7 Hz, 6H), 1.60–1.73 (m, 2H), 3.10–3.31 (m, 4H), 3.35–3.48 (m,

2H), 3.73–3.84 (m, 2H), 7.49 (s, 2H), 8.04 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.6, 18.4, 23.9, 28.0, 29.8, 30.3, 30.6, 30.66, 30.68, 30.76, 30.84, 30.88, 30.91, 33.2, 43.3, 46.7, 50.0, 115.9 (br), 119.2 (br), 125.0 (q, $J_{\text{C-F}} = 271$ Hz), 133.3 (q, $J_{\text{C-F}} = 33$ Hz), 143.3, 155.5, 158.5; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{43}\text{H}_{62}\text{F}_{12}\text{N}_7\text{O}_2$ 936.4773, found 936.4737.

Synthesis of guanidine-urea **62g**

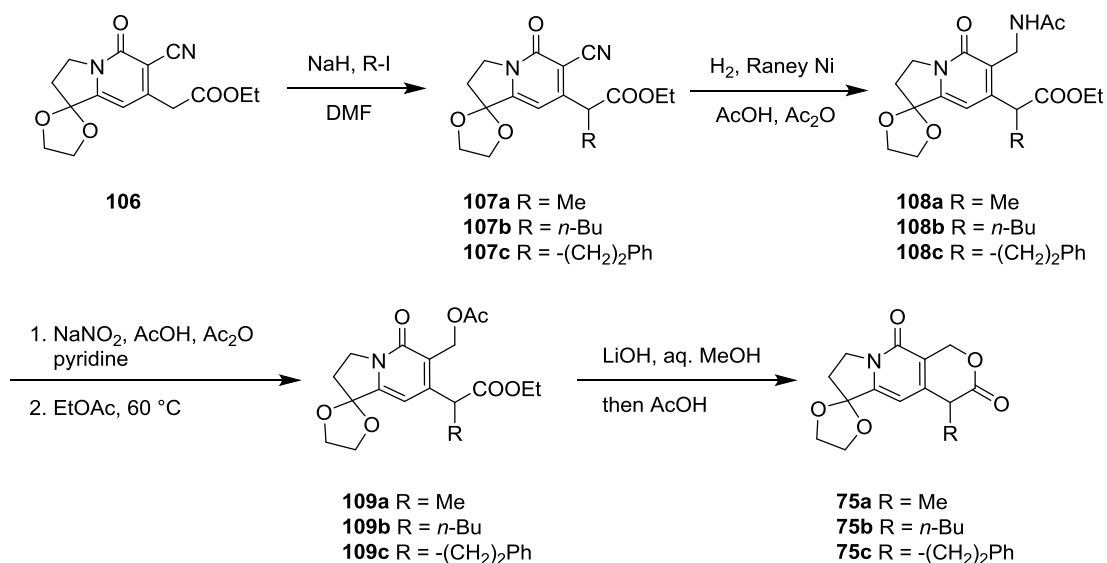


Guanidine-urea **62g**: According to the known procedure,^[40f,58] guanidine **105**^[40h] (100 mg, 0.14 mmol) was converted to 115 mg (82%) of compound **62g**: $[\alpha]_{\text{D}}^{20} = +63.7$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CD_3OD): δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.14–1.31 (m, 34H), 1.39–1.45 (t, $J = 10.1$ Hz, 2H), 1.53–1.63 (m, 2H), 1.68–1.76 (m, 2H), 1.80–1.86 (m, 2H), 3.29 (t, $J = 7.3$ Hz, 2H), 3.34–3.41 (m, 4H), 3.88–3.95 (m, 2H), 7.45 (s, 2H), 7.99 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.5, 21.68, 23.73, 27.76, 28.8, 30.0, 30.3, 30.47, 30.57, 30.6, 30.8, 33.1, 37.6, 40.0, 42.8, 44.6, 115.4, 118.9, 124.8 (q, $J_{\text{C-F}} = 271$ Hz), 133.1 (q, $J_{\text{C-F}} = 33$ Hz), 143.3, 155.7, 157.2; HRMS (ESI, $[\text{M}+\text{H}]^+$): calcd for $\text{C}_{45}\text{H}_{66}\text{F}_{12}\text{N}_7\text{O}_2$ 964.5086, found 964.5108.

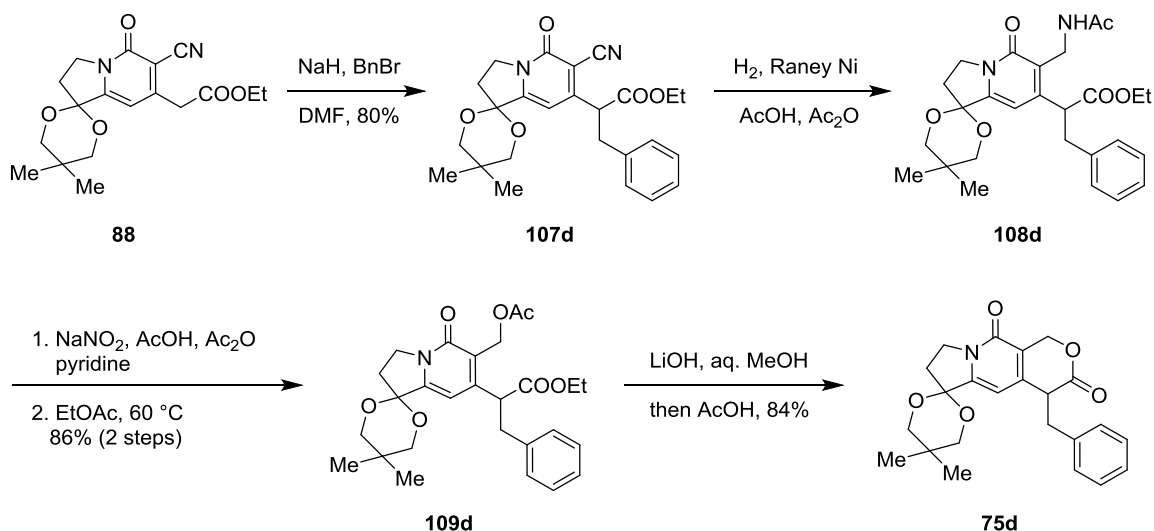
Synthesis of lactones **75a–75d**

Lactones **75a–75d** were synthesized from **106**^[15] or **88**^[35] according to the known procedure (Scheme S8).

a. Synthesis of lactone derivatives **75a–75c**



b. Synthesis of lactone derivative **75d**



Scheme S8. Synthesis of lactones **75a–75d**.

Nitrile **107a**: 97% yield; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.25 (t, $J = 6.9$ Hz, 3H), 1.5 (d, $J = 6.9$ Hz, 3H), 2.4 (t, $J = 6.9$ Hz, 2H), 4.10–4.21 (m, 9H), 6.31 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 13.9, 17.3, 33.4, 44.2, 45.3, 61.6, 61.7, 65.7, 65.8, 98.3, 103.7, 112.8, 114.4, 153.3, 158.5, 161.6, 171.2; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5\text{Na}$ 341.1113, found 341.1099.

Nitrile **107b**: 79% yield; ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.29–1.39 (m, 3H), 1.67–1.76 (m, 1H), 2.02–2.11 (m, 1H), 2.4 (t, $J = 6.9$ Hz, 2H), 3.99 (t, $J = 7.3$ Hz, 1H), 4.08–4.24 (m, 8H), 6.41 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.5, 13.8, 22, 29.1, 32.3, 33.3, 45.2, 49.8, 61.4, 65.6, 65.8, 98.3, 104.1, 112.6, 114.4, 153.1, 158.4, 160.4; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$ 383.1583, found 383.1558.

Nitrile **107c**: 71% yield; ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.3$ Hz, 3H), 1.99–2.08 (m, 1H), 2.36–2.46 (m, 3H), 2.57–2.74 (m, 3H), 4.05 (t, $J = 7.8$ Hz, 1H), 4.09–4.24 (m, 8H), 6.37 (s, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 14, 33.5, 34.3, 45.4, 49.8, 61.8, 65.8, 65.9, 98.4, 104.6, 112.9, 114.4, 126.3, 128.3, 128.5, 140.2, 153.2, 158.6, 160.1, 170.8; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$ 431.1583, found 431.1557.

Nitrile **107d**: 80% yield; ^1H NMR (400 MHz, CDCl_3): δ 0.89 (s, 3H), 1.14 (t, $J = 7.5$ Hz, 3H), 1.29 (s, 3H), 2.50–2.53 (m, 2H), 3.21 (ddd, $J = 9.2, 13.4, 180.4$ Hz, 2H), 3.60–3.69 (m, 4H), 4.05–4.18 (m, 4H), 4.31 (dd, $J = 6.9, 9.2$ Hz, 1H), 6.71 (s, 1H), 7.20–7.29 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3): δ 13.6, 21.7, 22.3, 28.6, 30, 38.3, 46, 51.8, 61.3, 72, 72.1, 99.3, 103.8, 104.9, 114.2, 126.6, 128.2, 128.6, 136.5, 153.2, 158.1, 159.5, 169.7; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_5\text{Na}$ 459.1896, found 459.1912.

Acetamide **108a**: 96% yield; ^1H NMR (400 MHz, CDCl_3): δ 1.21 (t, $J = 6.9$ Hz, 3H), 1.43 (d, $J = 7.3$ Hz, 3H), 1.92 (s, 3H), 2.37 (t, $J = 7.3$ Hz, 2H), 4.01–4.23 (m, 9H), 4.43 (q, $J = 7.3, 14.2$ Hz, 1H), 4.66 (dd, $J = 6.9, 14.2$ Hz, 1H), 6.25 (s, 1H), 6.67 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 13.8, 17.1, 22.7, 33.5, 35.2, 40.9, 44.3, 60.7, 65.1, 98.58, 112.6, 126.1, 146.7, 150.4, 161.1, 169.4, 172.9; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}$ 387.1532, found 387.1515.

Acetamide **108b**: 83% yield; ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 6.9$ Hz, 3H), 1.21 (t, $J = 7.3$ Hz, 3H), 1.24–1.37 (m, 3H), 1.58–1.67 (m, 1H), 1.92 (s, 3H), 1.97–2.08 (m, 1H), 2.38 (t, $J = 6.9$ Hz, 2H), 4.02–4.21 (m, 9H), 4.67 (dd, $J = 6.9, 14.2$ Hz, 2H), 6.6 (br, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.6, 13.8, 22.2, 22.8, 29.2, 31.8, 33.5, 35.2, 44.3, 46.7, 60.7, 65.1, 65.2, 98.8, 112.7, 126.5, 146.6, 149.4, 169.2, 172.5; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_6\text{Na}$ 429.2002, found 429.1986.

Acetamide **108c**: 93% yield; ^1H NMR (500 MHz, CDCl_3): δ 1.16 (t, $J = 6.9$ Hz, 3H), 1.84–1.93 (m, 4H), 2.29–2.36 (m, 3H), 2.52–2.66 (m, 2H), 3.40–4.14 (m, 8H), 4.34 (t, $J = 6.3$ Hz, 1H), 4.4 (dd, $J = 6.9, 14.3, 240.0$ Hz, 2H), 6.27 (s, 1H), 6.82 (br, 1H), 7.10–7.25 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 23, 33.5, 33.6, 34.1, 35.4, 44.5, 46.7, 61, 65.2, 65.3, 98.8, 112.8, 125.8, 126.8, 128.1, 128.2, 146.9, 149, 161.3, 169.4, 172.3; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_6\text{Na}$ 477.2002, found 477.1964.

Acetamide **108d**: ^1H NMR (400 MHz, CDCl_3): δ 0.90 (s, 3H), 1.11 (t, $J = 6.9$ Hz, 3H), 1.28 (s, 3H), 1.88 (s, 3H), 2.5 (t, $J = 7.3$ Hz, 2H), 2.98 (dd, $J = 6.9, 13.7$ Hz, 1H), 3.35 (dd, $J = 8.7, 13.7$ Hz, 1H), 3.64 (s, 2H), 3.67 (s, 2H), 3.18–4.48 (m, 6H), 4.57 (dd, $J = 7.3, 8.7$ Hz, 1H), 6.41 (br, 1H), 6.68 (s, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.8, 22, 22.5, 23, 29.4, 30.2, 35.2, 38.2, 45.1, 48.7, 60.9, 72.2, 72.3, 100, 105, 126.3, 127, 128.2, 129.1, 137.9, 147.1, 148.6, 161.1, 169.3, 171.6; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_6\text{Na}$ 505.2315, found 505.2269.

Acetate **109a**: 49% yield; ^1H NMR (500 MHz, CDCl_3): δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.42 (d, $J = 7.2$ Hz, 3H), 2.06 (s, 3H), 2.36 (t, $J = 6.9$ Hz, 2H), 3.97–4.19 (m, 9H), 5.24 (s, 2H), 6.24 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.8, 17.4, 20.6, 33.5, 41.3, 44.6, 57.5, 60.9, 65.2, 65.3, 98.1, 112.8, 122.8, 160.6, 170.6; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_7\text{Na}$ 388.1372, found 388.1344.

Acetate **109b**: 97% yield; ^1H NMR (300 MHz, CDCl_3): δ 0.87 (t, $J = 6.5$ Hz, 3H), 1.13–1.37 (m, 6H), 1.60–1.69 (m, 1H), 1.97–2.11 (m, 4H), 2.37 (t, $J = 6.9$ Hz, 2H), 3.82 (t, $J = 7.56$ Hz, 1H), 4.01–4.21 (m, 8H), 5.24 (s, 2H), 6.34 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.6, 13.9, 20.7, 22.2, 29.4, 32.1, 33.6, 44.7, 47, 57.5, 60.9, 65.2, 65.4, 98.3, 112.8, 123.4, 148.3, 152.2, 160.7, 170.7, 172.2; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_7\text{Na}$ 430.1842, found 430.1846.

Acetate **109c**: 96% yield; ^1H NMR (500 MHz, CDCl_3): δ 1.19 (t, $J = 6.9$ Hz, 3H), 1.86–1.93 (m, 1H), 1.99 (s, 3H), 2.31–2.41 (m, 3H), 2.50–2.65 (m, 2H), 3.88 (t, $J = 6.9$ Hz, 1H), 4.03–4.18 (m, 8H), 5.11 (d, $J = 11.5$ Hz, 1H), 5.17 (d, $J = 11.5$ Hz, 1H), 6.31 (s, 1H), 7.11 (d, $J = 6.9$ Hz, 2H), 7.16 (t, $J = 7.45$ Hz, 1H), 7.23 (d, $J = 7.45$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 14, 20.8, 33.5, 33.6, 34.1, 44.8, 46.7, 57.6, 61.2, 65.3, 65.4, 112.9, 123.6, 126.1, 128.1, 128.3, 140.6, 148.6, 151.9, 160.7, 170.6, 171.9; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_7\text{Na}$ 478.1842, found 478.1840.

Acetate **109d**: 86% yield in 2 steps; ^1H NMR (400 MHz, CDCl_3): δ 0.90 (s, 3H), 1.12 (t, $J = 6.9$ Hz, 3H), 1.29 (s, 3H), 2 (s, 3H), 2.44–2.55 (m, 2H), 2.91 (dd, $J = 6.9, 13.7$ Hz, 1H), 3.33 (dd, $J = 8.7, 13.7$ Hz, 1H), 3.64 (d, $J = 4.6$ Hz, 2H), 3.67 (s, 2H), 3.99–4.21 (m, 5H), 5 (d, $J = 11.9$ Hz, 1H), 5.07 (d, $J = 11.9$ Hz, 1H), 6.89 (s, 1H), 7.15=7.25 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.7, 20.7, 22, 22.5, 29.3, 30.2, 38.4, 49.1, 57.5, 61, 72.1, 72.3, 99.4, 105.1, 123.8, 126.5, 128.3, 128.7, 137.8, 148.7, 151.5, 160.6, 170.6, 171.4; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_7\text{Na}$ 506.2155, found 506.2112.

Lactone **75a**: 58% yield; ^1H NMR (500 MHz, CDCl_3): δ 1.27 (d, $J = 7.3$ Hz, 3H), 2.4 (t, $J = 6.9$ Hz, 2H), 3.5 (q, $J = 6.9$ Hz, 1H), 4.10–4.21 (m, 6H), 5.24 (d, $J = 15.6$ Hz, 1H), 5.43 (d, $J = 15.6$ Hz, 1H), 6.19 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 14.4, 31.0, 33.9, 38.6, 44.7, 64.9, 65.5, 65.6, 97.3, 112.9, 120.4, 148.0, 149.1, 157.5, 171.8; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_5\text{Na}$ 300.0848, found 300.0898.

Lactone **75b**: 85% yield; ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.22–1.45 (m, 4H), 1.85–1.91 (m, 1H), 3.47 (t, $J = 6.9$ Hz, 1H), 5.24 (d, $J = 16$ Hz, 1H), 5.45 (d, $J = 16$ Hz, 1H), 6.09 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.4, 22.0, 28.5, 31.1, 33.6, 44.3, 44.4, 65.4, 98.5, 98.6, 112.6, 119.6, 147.0, 148.6, 157.4, 170.7; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5\text{Na}$ 342.1317, found 342.1295.

Lactone **75c**: 62% yield; ^1H NMR (400 MHz, CDCl_3): δ 2.12–2.28 (m, 2H), 2.4 (t, $J = 6.9$ Hz, 2H), 2.76 (t, $J = 8.2$ Hz, 2H), 3.51 (t, $J = 6.4$ Hz, 1H), 4.07–4.18 (m, 6H), 5.29 (d, $J = 16$ Hz, 1H), 5.43 (d, $J = 16$ Hz, 2H), 6.06 (s, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 32.1, 32.3, 33.4, 43.4, 44.3, 65.1, 65.2, 98.0, 98.2, 112.5, 119.7, 125.9, 128.0, 139.7, 146.5, 148.6, 157.1, 170.3; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_5\text{Na}$ 390.1317, found 390.1279.

Lactone **75d**: 84% yield; ^1H NMR (500 MHz, CDCl_3): δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.22–1.45 (m, 4H), 1.85–1.91 (m, 1H), 3.47 (t, $J = 6.9$ Hz, 1H), 5.24 (d, $J = 16$ Hz, 1H), 5.45 (d, $J = 16$ Hz, 1H), 6.09 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 22.0, 22.5, 29.3, 30.3, 38.6, 45.3, 46.1, 65.9, 72.3, 72.4, 99.7, 105.1, 120.8, 127.4, 128.6, 129.2, 135.7, 148.8, 157.2, 170.6; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5\text{Na}$ 418.1630, found 418.1597.

Asymmetric α -hydroxylation of lactone **60** or **75a–75d** using guanidine-urea bifunctional organocatalyst **62**

General Procedure for catalytic asymmetric α -hydroxylation of pyranoindolizine derivatives **60** or **75a–75d** using guanidine-urea bifunctional organocatalysts **62**:

A test tube equipped with a magnetic stirring bar was charged with catalyst **10** (0.01 mmol), pyranoindolizine derivative **8** (0.1 mmol), K_2CO_3 (0.1 mmol) and toluene (1.0 mL) at room temperature. The mixture was cooled to 0 °C and stirred for 10 minutes. Then, cumene hydroperoxide (0.15 mmol) was added to it, and the whole was stirred at 0 °C for 24 h. The reaction was quenched by addition of $Na_2S_2O_3$ solution (10%, 2 mL) and acetic acid (0.2 mL), and the mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted three times with $CHCl_3$. The combined organic solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 1/1 to $CHCl_3/CH_3OH$ = 100/1) to give the product **6**. The enantiomeric excess and the absolute configuration were determined by HPLC analysis of the product using a chiral column (DAICEL Chiralpak IA) with *n*-hexane/ethanol as the eluent.

α -Hydroxy lactone **46**: For details of the spectral data of α -hydroxy lactone **46**, see the reference 21b. Enantiomeric excess of **46** was determined by chiral HPLC analysis: DAICEL Chiralpak IA column (250 \times 4.6 mm), *n*-hexane/ethanol = 60/40, flow rate 1 mL/min, λ = 220 nm, τ_1 = 18.93 (major), τ_2 = 24.92 (minor).

α -Hydroxy lactone **76a**: 99% yield; $[\alpha]_D^{25}$ = +66.6 (*c* 1.0, $CHCl_3:CH_3OH$ = 1:1); 1H NMR (500 MHz, $CDCl_3$): δ 1.27 (d, *J* = 7.3 Hz, 3H), 2.4 (t, *J* = 6.9 Hz, 2H), 3.5 (q, *J* = 6.9 Hz, 1H), 4.10–4.21 (m, 6H), 5.24 (d, *J* = 15.6 Hz, 1H), 5.43 (d, *J* = 15.6 Hz, 1H), 6.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.9, 33.9, 44.8, 65.5, 65.8, 66.0, 95.8, 113.0, 118.1, 149.8, 150.2, 157.4, 174.5; HRMS (ESI, $[M+Na]^+$): calcd for $C_{14}H_{15}N_1O_6Na$ 316.0797, found 316.0784. Enantiomeric excess of **76a** was determined to be 75% ee by chiral HPLC analysis: DAICEL Chiralpak IA column (250 \times 4.6 mm), *n*-hexane/2-propanol = 70/30, flow rate 1 mL/min, λ = 220 nm, τ_1 = 20.20 (major), τ_2 = 15.91 (minor).

α -Hydroxy lactone **76b**: 95% yield; $[\alpha]_D^{25}$ = +75.9 (*c* 0.91, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.6 Hz, 3H), 1.22–1.39 (m, 3H), 1.67–1.81 (m, 3H), 2.42

(t, $J = 6.9$ Hz, 2H), 3.74 (s, 1H), 4.07–4.23 (m, 6H), 5.17 (d, $J = 16$ Hz, 1H), 5.61 (d, $J = 16$ Hz, 1H), 6.57 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 13.7, 22.3, 25.2, 33.8, 37.8, 44.7, 65.4, 65.5, 66.1, 72.2, 96.6, 112.9, 118.2, 149.2, 150.0, 157.4, 173.7; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_6\text{Na}$ 358.1267, found 358.1222. Enantiomeric excess of **76b** was determined to be 82% ee by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/2-propanol = 70/30, flow rate 1 mL/min, $\lambda = 220$ nm, $\tau_1 = 26.51$ (major), $\tau_2 = 17.35$ (minor).

α -Hydroxy lactone **76c**: 90% yield; $[\alpha]_{\text{D}}^{25} = +13.3$ (c 0.92, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 1.96–2.12 (m, 2H), 2.42 (t, $J = 6.9$ Hz, 2H), 2.66–2.76 (m, 2H), 3.87 (s, 1H), 4.08–4.25 (m, 6H), 5.19 (d, $J = 16$ Hz, 1H), 5.64 (d, $J = 16$ Hz, 1H), 6.62 (s, 1H), 7.12 (d, $J = 6.9$ Hz, 2H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 29.5, 33.8, 39.6, 44.8, 65.5, 65.6, 66.2, 72.1, 96.6, 112.9, 118.3, 126.2, 128.2, 128.4, 140.0, 149.4, 149.6, 157.4, 173.5; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_6\text{Na}$ 406.1266, found 406.1222. Enantiomeric excess of **76c** was determined to be 82% ee by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/2-propanol = 70/30, flow rate 1 mL/min, $\lambda = 220$ nm, $\tau_1 = 32.06$ (major), $\tau_2 = 25.84$ (minor).

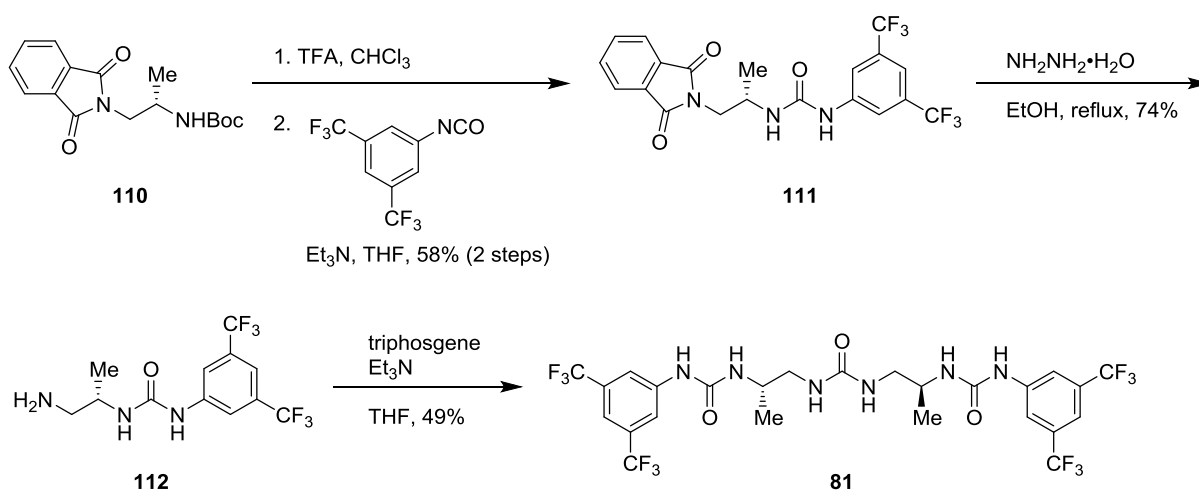
α -Hydroxy lactone **76d**: 99% yield; $[\alpha]_{\text{D}}^{25} = +26.7$ (c 0.55, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 0.90 (s, 3H), 1.26 (s, 3H), 2.48–2.58 (m, 2H), 3.09 (q, $J = 13.2, 30.9$ Hz, 2H), 3.65 (s, 2H), 3.67 (s, 2H), 4.09–4.19 (m, 2H), 4.63 (d, $J = 16$ Hz, 1H), 5.46 (d, $J = 16$ Hz, 1H), 6.72 (s, 1H), 7.06–7.08 (m, 2H), 7.26–7.27 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 22.1, 22.5, 29.8, 30.3, 45.4, 46.0, 66.2, 72.2, 72.3, 72.8, 97.6, 105.0, 119.2, 127.6, 128.2, 130.1, 132.8, 148.2, 149.2, 157.0, 172.9; HRMS (ESI, $[\text{M}+\text{Na}]^+$): calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_6\text{Na}$ 434.1580, found 434.1561. Enantiomeric excess of **76d** was determined to be 80% ee by chiral HPLC analysis: DAICEL Chiralpak IA column (250×4.6 mm), *n*-hexane/ethanol = 60/40, flow rate 1 mL/min, $\lambda = 220$ nm, $\tau_1 = 19.52$ (major), $\tau_2 = 11.60$ (minor).

Synthesis of (+)-C20-desethylbenzyl camptothecin (79)

Synthesis of (+)-C20-desethylbenzyl camptothecin (79): A solution of compound **76d** (822 mg, 2.0 mmol, 80% ee) in 80% aqueous TFA (25 mL) was stirred at room temperature for 1 hour. The mixture was diluted with water, and then extracted with CHCl_3 . The organic extract was dried over MgSO_4 , filtered, and then evaporated

under reduced pressure to give ketone **77**, which was used in the next step without purification. A mixture of crude ketone **4e**, 2-aminobenzaldehyde dimethylacetal (**78**) (6.0 mmol), *p*-TsOH (0.02 mmol), and toluene (40 mL) was refluxed for 18 hours using a Dean-Stark trap under a nitrogen atmosphere, and then the reaction mixture was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (CHCl₃/ethyl acetate = 2:1 to 1:1) to give a brown solid. The solid was recrystallized from methanol/acetonitrile to give (+)-C20-desethylbenzyl camptothecin (**79**) (130mg, 16%, 2 steps): mp 247–250 °C (dec.); [α]_D²⁶ = +54.8 (*c* 0.5, DMF); ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.19 (dd, *J* = 13.3, 61.8 Hz, 2H), 3.51 (s, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 5.23–5.36 (m, 3H), 6.81 (s, 1H), 7.06–7.07 (m, 2H), 7.18–7.20 (m, 3H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 8.13 (t, *J* = 7.8 Hz, 2H), 8.68 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 44.3, 50.1, 65.3, 72.9, 96.9, 119.6, 127.0, 127.6, 127.8, 128.4, 129.0, 129.6, 130.3, 130.4, 131.5, 134.0; HRMS (ESI, [M+Na]⁺): calcd for C₂₅H₁₈N₂O₄Na 433.1164, found 434.1208. Enantiomeric excess of **79** was determined to be >99% ee by chiral HPLC analysis: DAICEL Chiralpak IA column (250 × 4.6 mm), *n*-hexane/ethanol = 60/40, flow rate 0.2 mL/min, λ = 220 nm, τ₁ = 24.72 (major), τ₂ = 23.61 (minor).

Synthesis of triurea **81**



Scheme S9. Synthesis of triurea **81**.

Urea **111**: To a solution of **110**^[60] (1.57 g, 5.16 mmol) in CHCl₃ (15 mL) was added TFA (3 mL) at room temperature. The mixture was stirred at room temperature for 3 hours, and then evaporated under reduced pressure. To a solution of the residue in

THF (15 mL) were added Et₃N (1.10 mL, 7.89 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate (0.99 mL, 5.70 mmol) at room temperature. The whole mixture was stirred at room temperature for 3 days, and then evaporated under reduced pressure. A solution of the residue in CHCl₃ (30 mL) was washed with water (20 mL), and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (45 g, CHCl₃/ethyl acetate = 95/5 to 3/1) to give 1.37 g (58%) of **111** as a colorless solid: mp 178–179 °C; [α]_D²⁹ = +14.5 (*c* 1.3, DMSO); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.18 (d, *J* = 6.7 Hz, 3H), 3.67 (d, *J* = 6.7 Hz, 2H), 4.00–4.21 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 7.48 (s, 1H), 7.76–7.89 (m, 6H), 9.1 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 18.1, 43.0, 44.3, 113.4 (br), 117.3 (br), 122.9, 123.2 (q, *J*_{C-F} = 273 Hz), 130.5 (q, *J*_{C-F} = 33 Hz), 131.6, 134.2, 142.3, 154.4, 168.1; MS (APCD): *m/z* 460 [M+H]⁺; elemental analysis calcd (%) for C₂₀H₁₅N₃O₃F₆: C, 52.30; H, 3.29; N, 9.15; F, 24.82; found: C, 52.26; H, 3.15; N, 9.08; F, 24.62.

Amine 112: To a solution of urea **111** (1.31 g, 2.85 mmol) in ethanol (10 mL) and THF (6 mL) was added hydrazine hydrate (0.56 mL, 11.5 mmol) at 50 °C, and then the resulting mixture was refluxed for 6 hours. Insoluble materials were collected by filtration and washed with ethanol. The filtrate and washing were combined and evaporated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (30 g, CHCl₃ to CHCl₃/CH₃OH = 9/1) to give 697 mg (74%) of **112** as a colorless solid: mp 141–142 °C; [α]_D²⁸ = –3.5 (*c* 1.0, CH₃OH); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.07 (d, *J* = 6.7 Hz, 3H), 1.63 (br, 2H), 2.56 (dd, *J* = 5.7, 12 Hz, 1H), 2.58 (dd, *J* = 5.7, 12 Hz, 1H), 3.56–3.68 (m, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 7.52 (s, 1H), 8.05 (s, 2H), 9.17 (br, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 18.3, 46.7, 47.5, 113.1 (br), 117.0 (br), 123.3 (q, *J*_{C-F} = 272.4 Hz), 130.6 (q, *J*_{C-F} = 32.8 Hz), 142.7, 154.4; MS (ESI): *m/z* 330 [M+H]⁺; elemental analysis calcd (%) for C₁₂H₁₃N₃OF₆•0.22 H₂O: C, 43.26; H, 4.07; N, 12.61; F, 34.21; found: C, 43.65; H, 3.84; N, 12.63; F, 33.85.

Triurea 81: To a solution of amine **112** (221 mg, 0.48 mmol) in THF (5 mL) were added Et₃N (0.075 mL, 0.54 mmol) and triphosgene (30 mg, 0.10 mmol) on ice-bath. The reaction mixture was stirred at room temperature for 3 days, and then diluted with water. A separated precipitate was collected by filtration, washed with water, and then air-dried to give 81 mg (49%) of triurea **81** as a colorless solid: mp 246–248 °C; [α]_D³¹ = –7.4 (*c* 1.1, DMSO); ¹H NMR (400 MHz, CD₃OD): δ 1.15 (d, *J* = 6.7 Hz, 6H), 3.12–3.27 (m, 4H), 3.80–3.90 (m, 2H), 7.44 (s, 2H), 7.96 (s, 2H); ¹³C NMR (100 MHz,

CD₃OD): δ 18.8, 46.5, 48.1, 115.5 (br), 119.0 (br), 124.8 (q, $J_{C-F} = 272$ Hz), 133.1 (q, $J_{C-F} = 33$ Hz), 143.4, 157.1, 161.8; HRMS (ESI, $[M+Na]^+$): calcd for C₂₅H₂₄F₁₂N₆O₃Na 707.1616, found 707.1584.

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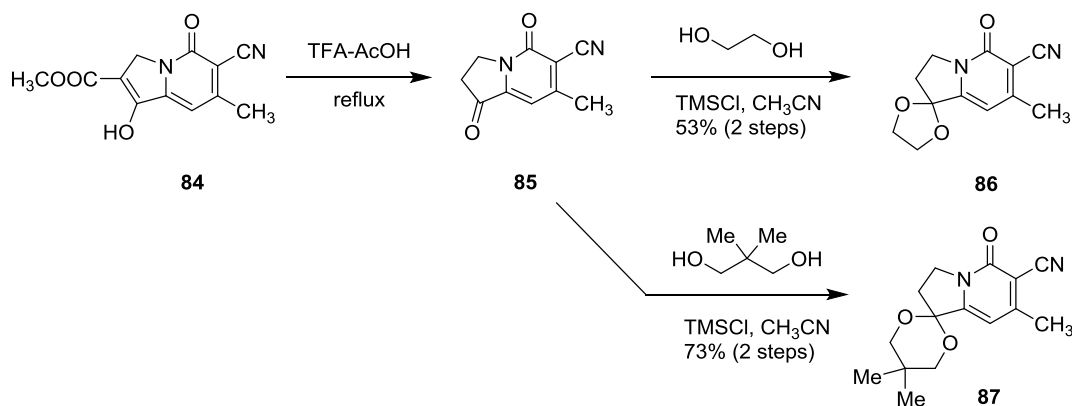
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- [30] C2 位ケトンの環状アセタール化を検討した結果、エチレングリコールを用いた場合には **86** を 53%収率で得た。一方、ネオペンチルグリコールを用いた場合には、**87** を 73%収率で得ることができた。



- [31] クロロエステル **63a** の合成については、実験項にその詳細を記載した。
- [32] 光学活性カルボン酸(*R*)-**33j** の合成については、実験項にその詳細を記載した。
- [33] (-)-**32k** から(*S*)-**14** への誘導については、その詳細を実験項に記載した。
- [34] アミノケトン **65** は、市販の *p*-アニシジンから 3 工程、総収率 41%で合成した。詳細については実験項に記載した。
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