医薬有用分子の効率的創出を志向した
新規 Friedel-Crafts 型反応の開発

2016 年

鈴木　雄太

序論

（ここは何を切るべきか…場を良く見ろ。思い出せ、奴の仕草を。どこで待っている？）…わかる人には伝わるだろう。そう、麻雀だ。冒頭の文言からも想像されるように、麻雀は人の記憶力や心理が如実に問われる、頭の体操にはもってこいのゲームである。無論、筆者も（研究に差し障りがない程度に）麻雀をこよなく愛する一人だ。一見、博士論文には相応しくない趣味の話かと思われるかもしれないが、何卒お付き合い頂きたい。

麻雀を嗜むに当たり、何より欠かせないのが「観察力」と「分析力」である。目まぐるしく展開する場の中で、相手の打ち回しや切り方等あらゆる情報を把握しなければならない。そういった細かい情報をもとに残り牌や自分の手牌と相談し、上手に場を切り抜けられる手を作り上げていく。まぁ実際は多分に運の要素が絡んでくるので、なかなか思うように進まないことがほとんどである。しかし、相手の待ちが見事に予想通りであった時や自分の思い通りの手を上がった時は、自分の情報分析が正しかったと自信が湧く。こうして成功体験を繰り返していくことで得られた自信が、そのまま麻雀の実力となっていく。

この「観察力」と「分析力」を駆使して事を成し遂げるという点において、麻雀と研究とは似通っていると筆者は感じる。日々の実験や論文調査により得た情報を良く考察し、そこから生み出した仮説をベースに次なる実験計画を立てる――研究はこの作業の繰り返しである。打ち立てた仮説は多くの場合無に帰してしまうが、ごく稀に期待通りの結果を与える。このように、気の遠くなるような検討とやる気を削がれるような結果を繰り返し、それでも考えることを諦めなかったが故に得た成功は、極上の喜びとなる。価値を見出せず、時には意味の無いように感じるかもしれない研究を続けていくためには、その成功の際に感じる喜びをモチベーションとすることが大切である。

本論の第二章に記載した、研究進展のブレイクスルーとなった白金触媒のアイデアは、筆者自身が論文の細かい情報を頭の片隅に記憶していたからこそ産み出すことが出来た。実の所、このアイデア行き着くまで１年以上の歳月を費やしており、その間は研究のみならず私生活においても気が滅入る出来事の連続だった。しかし、そのような状況下で自分を見失うことなく、微かな情報を足掛かりに希望を手繰り寄せることが出来たのはきっと、日々麻雀で「観察力」と「分析力」に磨きをかけていたからであろう。決して頭脳明晰でも勤勉でもない筆者だが、情報収集と創意工夫を心掛けていたからこそ、ある程度の研究成果を残すことができたように思う。常日頃からアンテナを張り、膨大な情報をほんの一部でも記憶すること。そして、考えを巡らせる行為を楽しむこと。この意識が成功への近道となると筆者は信じている。

本論文に書き起こした内容が、誰かの成功に繋がる情報となることを期待したい。

目次

略語表

便宜上、本論文全般において以下に示す略語、および略称を用いた。

AAA	asymmetric allylic alkylation
Ac	acetyl
(*R,R*)-ANDEN-phenyl Trost ligand	(+)-(11*R*,12*R*)bis[2′-(diphenylphosphino)benzamido]-9,10-dihydro-9,10-ethanoanthracene
Ar	aryl
Bn	benzyl
Boc	tert-butoxycarbonyl
BSA	N,O-bis(trimethylsilyl)acetamide
i-Bu	isobutyl
n-Bu	normal butyl
s-Bu	secondary butyl
t-Bu	tertiary butyl
Bz	benzoyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
(*R,R*)-DACH-phenyl Trost ligand	(1*R*,2*R*)-(+)-1,2-diaminocyclohexane-N,N′-bis(2-diphenylphosphinobenzoyl)
dba	dibenzylidenacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DPEphos	Bis[2-(diphenylphosphino)phenyl] ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane

dppf	1,1’-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
EI	electron ionization
eq	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato
h	hour
*c*Hex	cyclohexyl
HFIP	1,1,1,,3,3,3-hexafluoroisopropanol
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons reaction
L	ligand
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	mol/L
m	meta
Me	methyl
MOM	methoxymethyl
(*R*)-MonoPhos	(*R*)-(–)-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine
(*S*)-MOP	(*S*)-(–)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl
Ms	methanesulfonyl
MS 4A	molecular sieves, 4A
(*S*)-(–)-9-NapBN	(1*S*,2*R*,5*S*,6*R*)-2,6-dimethyl-9-(1-naphthyl)-9-phosphabicyclo-[3.3.1]nonane
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
n.r.	no reaction

o	ortho
p	para
Ph	phenyl
(*S*)-PHOX	(4*S*)-(–)-4,5-dihydro-2-[2'-(diphenylphosphino)phenyl]-4-isoprop yloxazole
pin	pinacolato
Piv	pivaloyl
PMB	para-methoxybenzyl
i-Pr	isopropyl
py	pyridine
quant.	quantitative yield
R	rectus
RuPhos	2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl
rt	room temperature
S	sinister
SES	2-[(trimethylsilyl)ethyl]sulfonyl
SM	starting material
SN1	unimolecular nucleophilic substitution
SN2	bimolecular nucleophilic substitution
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
temp.	Temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N’,N’-tetramethylethylenediamine
TMS	Trimethylsilyl
TPS	2,4,6-triisopropylbenzenesulfonyl
Ts	para-toluenesulfonyl
UV	Ultraviolet
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

第一章　分子内 Friedel–Crafts 型アリル位アルキル化反応による 9,10-ジヒドロフェナントレン類の新規触媒的不斉合成法の開発

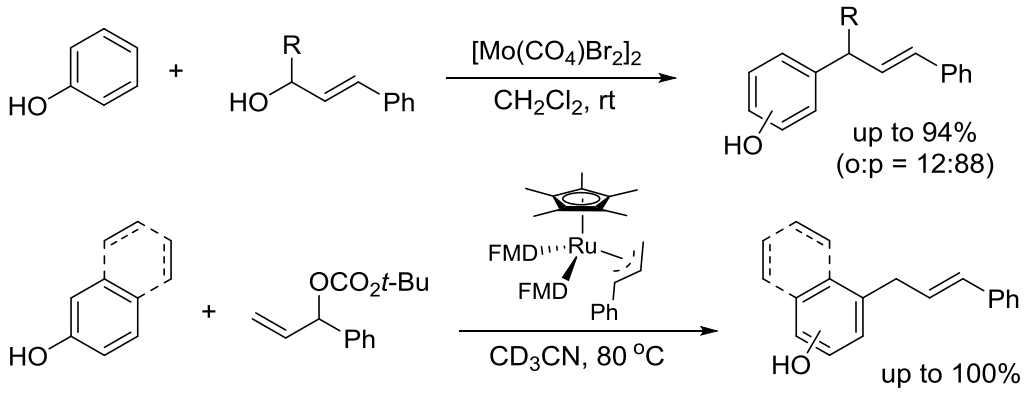
第一節　背景

近年、遷移金属触媒を用いて芳香族 C–H 結合を直接的に官能基化する有機合成手法――いわゆる C–H activation の開拓に大きな注目が集まっている。これらは工程数の短縮や副生成物低減による環境負荷の抑制などといった点において非常に魅力的な手法となっている。しかしながら一般的に Ru などの希少金属触媒下、配向性置換基の存在や過激な反応条件が必要であり、未だ実用性に欠ける反応であることは否めない。

一方で、古典的な合成手法である Friedel–Crafts 反応は、メカニズムこそ異なるものの、本質的には芳香環の C–H 結合を直接的に官能基化させる反応であり、反応条件も幅広く設定できる点で実用に適う有機合成反応であると言える。

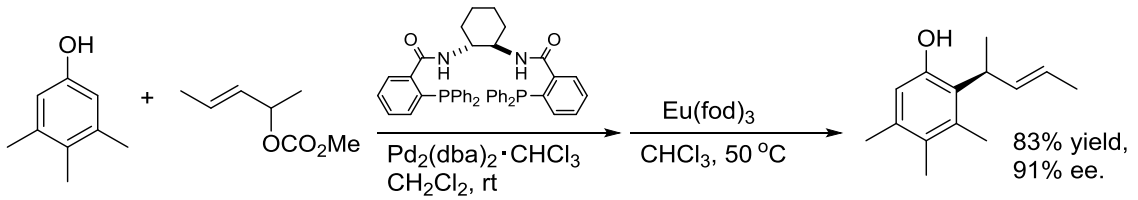
遷移金属触媒によるアリル位アルキル化反応はフェノール類を求核剤として用いた場合、一般的にその酸素原子上で置換反応が進行することが知られている [1]。しかし、芳香環の炭素原子上における Friedel–Crafts 型のアリル位置換反応は、調べ得る限り下図に示す Mo[2] や Ru[3] を用いた報告例が存在するのみである。また、これらの例はいずれもラセミ反応であり、触媒的不斉反応に関しての報告例は存在しない。

Scheme 1-1. Transition metal-catalyzed *C*-allylation of phenols



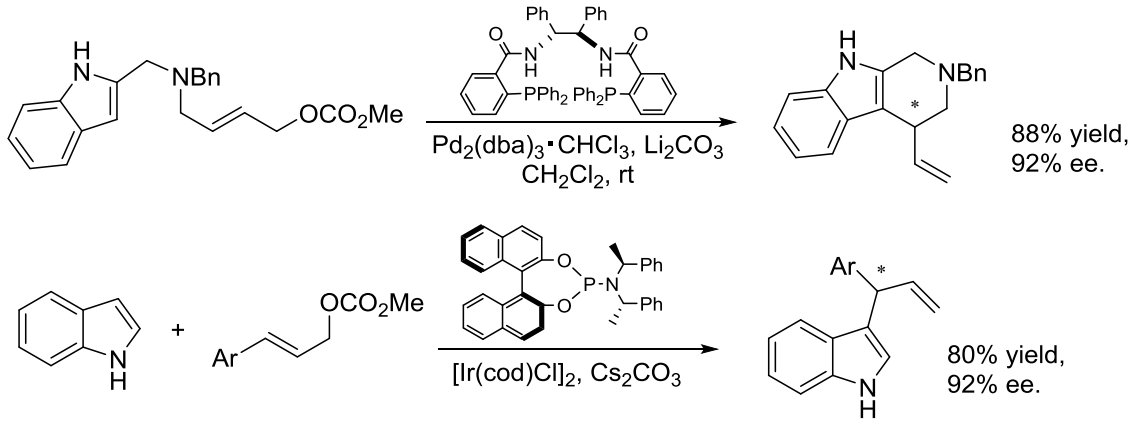
なお、Pd 触媒による不斉 *O*-アリル化の後、Claisen 転位によって間接的にキラルな *C*-アリル化体を得ている反応の報告例はあるが、フェノール類の炭素原子に対して直接的にアリルユニットを導入できる触媒的不斉反応は存在しない [4]。

Scheme 1-2. Pd-catalyzed *C*-allylation of phenols via *O*-allylation–Claisen rearrangement sequence



一方で、インドール等の電子豊富な芳香族ヘテロ環を求核剤として用いた触媒的不斉アリル位アルキル化反応については、いくつか報告例が存在する [5,6]。

Scheme 1-3. Transition metal-catalyzed asymmetric *C*-allylation of indoles

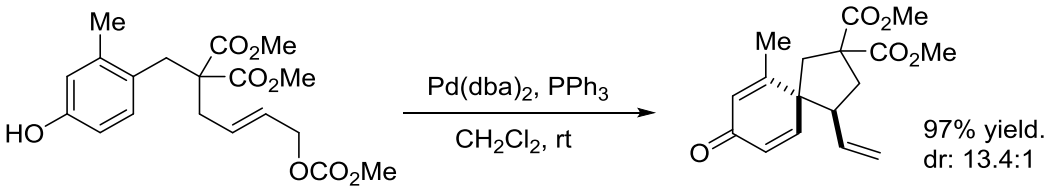


これらのインドールに関する報告例に鑑みれば、フェノール類を求核剤として用いた場合にも基質と条件を適切に設定することで *C*-アリル化体をエナンチオ選択的に与える可能性が期待される。

第二節　当研究室におけるこれまでの研究成果

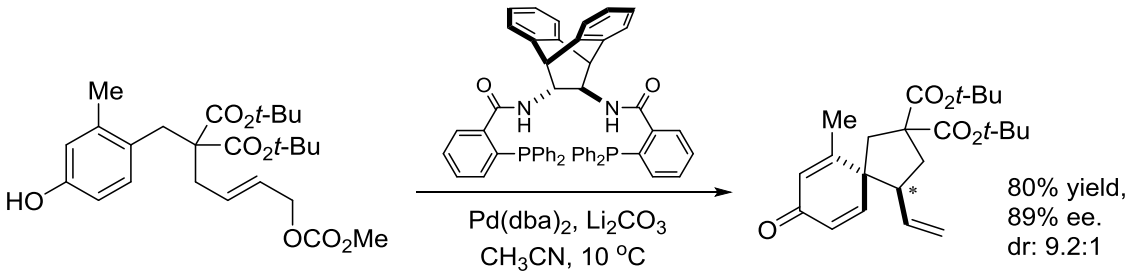
当研究室の石毛は下図に示す側鎖にアリルカーボネート部位を組み込んだパラ置換型フェノール誘導体を設計し、分子内 *ipso*-Friedel–Crafts 型アリル位アルキル化反応の検討を行った。結果、本基質に Pd 触媒を作用させることで期待通りの反応が効率的に進行することを見出し、スピロシクロヘキサジエノン類の新規合成法の開発に成功した[7]。本反応はカーボネートが脱離する際に生じるメトキシドアニオンがフェノール性水酸基を十分に脱プロトン化するため、塩基の添加が不要である。

Scheme 1-4. Synthesis of spirocyclohexadienones using intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols



また、当研究室の吉田はキラル配位子や添加剤の入念な検討により、本反応の不斉化に成功した[8]。しかしながら、本反応はメタ位置換基が選択性に大きく影響を与えることがわかっており、良好な光学収率を与える基質は限られている。

Scheme 1-5. Pd-cataryzed asymmetric intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols

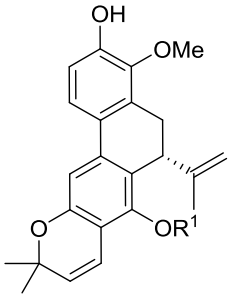


以上、当研究室ではフェノール類の触媒的分子内 *ipso*-Friedel–Crafts 型アリル位アルキル化反応によるスピロシクロヘキサジエノン類の合成に関して精力的に研究活動を行ってきた。

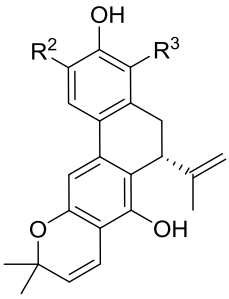
第三節　研究目的

高度に酸素官能基化されたプレニル化ポリフェノール類は天然に頻出する構造であり、これら天然物の中には生物活性を有するものが数多く存在する。例えば 1991 年に柿崎らによって単離、構造決定された Cedrelin A は黄色ブドウ球菌(209P)や枯草菌(IAM1213)に対する抗菌活性を示し、1987 年に Monache らによって単離された Paralycolin A は KB 細胞や P388 細胞に対する抗癌活性を示すことが報告されている[9]。これら天然物はジヒドロフェナントレン芳香環上に多数存在する酸素官能基に加えて、10 位に共通してイソプロペニル基を持つ。すなわち、本骨格は医薬品シードと成り得る可能性を秘めているため、その効率的かつ自由度の高い合成法の開発により創薬研究への貢献が期待できる。

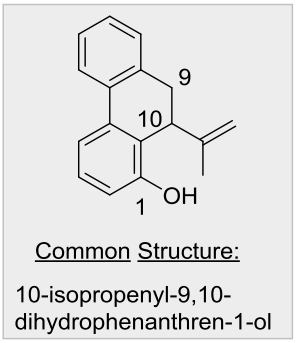
Figure 1-1. Natural products with a 10-isopropenyl-9,10-dihydrophenanthren-1-ol skeleton



Cedrelin A
(R^1 = H)
Cedrelin B
(R^1 = CH_3)



Paralycolin A
(R^2 = H, R^3 = OH)
Paralycolin B
(R^2 = OH, R^3 = H)



Cytotoxic activity
Cedrelin A: *Staphylococcus aureus* (209P) and *Bacillus subtillis* (IAM1213).
Paralycolin A: KB and P388 cells.

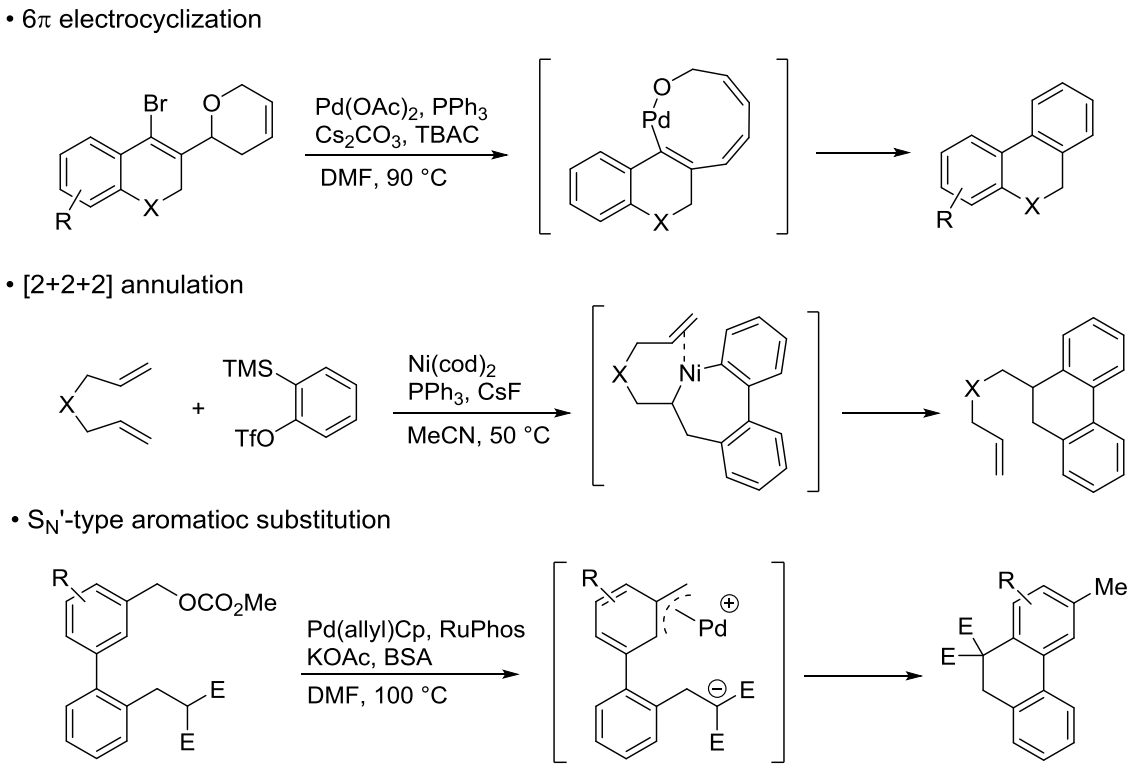
9,10-ジヒドロフェナントレン類の効率合成に関しては、近年いくつかの報告がなされている[10]。遷移金属触媒を用いた例を以下に紹介する。

Ray らは Pd 触媒を用いた 6π電子環状反応により、9,10-ジヒドロフェナントレン骨格を合成した[10b]。本反応は基質のビニルハライドが Pd 触媒へと酸化的付加した後、分子内エーテル結合への挿入を経て生じた九員環パラダサイクル中間体が、6π電子環状反応を受けることでジヒドロフェナントレンへと導かれる。

佐藤らは Ni 触媒を用いて、２当量のベンザイン中間体とジエンの[2+2+2]環化付加により 9,10-ジヒドロフェナントレン骨格を合成している。

また、桑野らはベンジルカーボネート誘導体に対する分子内 S_N'型芳香族置換反応により本骨格を合成している。

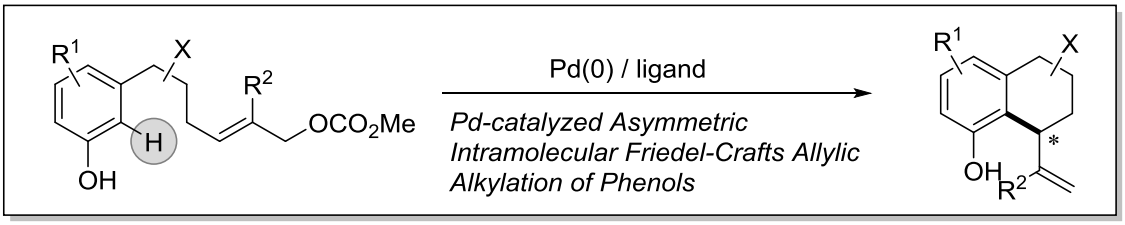
Scheme 1-7. Efficient catalytic synthesis of 9,10-dihydrophenanthrene frameworks



しかし、これらはいずれもラセミ反応のあり、10 位に不斉点を導入するのは困難である。

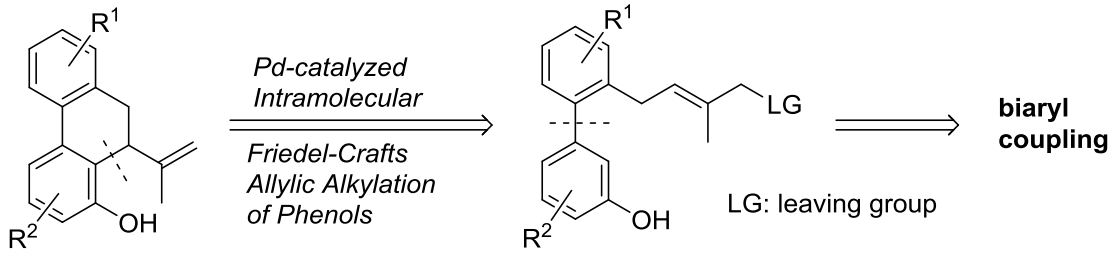
分子内 Friedel–Crafts 型アリル位アルキル化反応はメタ置換型フェノール誘導体を基質とした場合、芳香環オルト位或いはパラ位 C–H 結合の直接変換によりアリル基ユニットの導入された双環状分子を構築可能である。また、本反応はキラル配位子のスクリーニングにより容易に不斉化が見込める。

Scheme 1-6. Pd-cataryzed intramolecular Friedel–Crafts allylic alkylation of *meta*-substituted phenols



そこで、本反応形式を下図に示すフェニルフェノール誘導体へと応用できれば、天然物の共通母骨格である 9,10-ジヒドロフェナントレン構造と側鎖のイソプロペニル基を一挙に構築できると予想した。本反応は、その基質自体もクロスカップリングを用いる収束型合成により簡便に調製できるため、上下芳香環に種々の官能基が導入されたバリエーション豊富なジヒドロフェナントレン類の迅速合成が期待できる。さらに適切なキラル配位子の選択により 10 位の不斉点も制御できれば、生物活性天然物の触媒的不斉全合成も可能となる。

Scheme 1-7. Synthetic plan

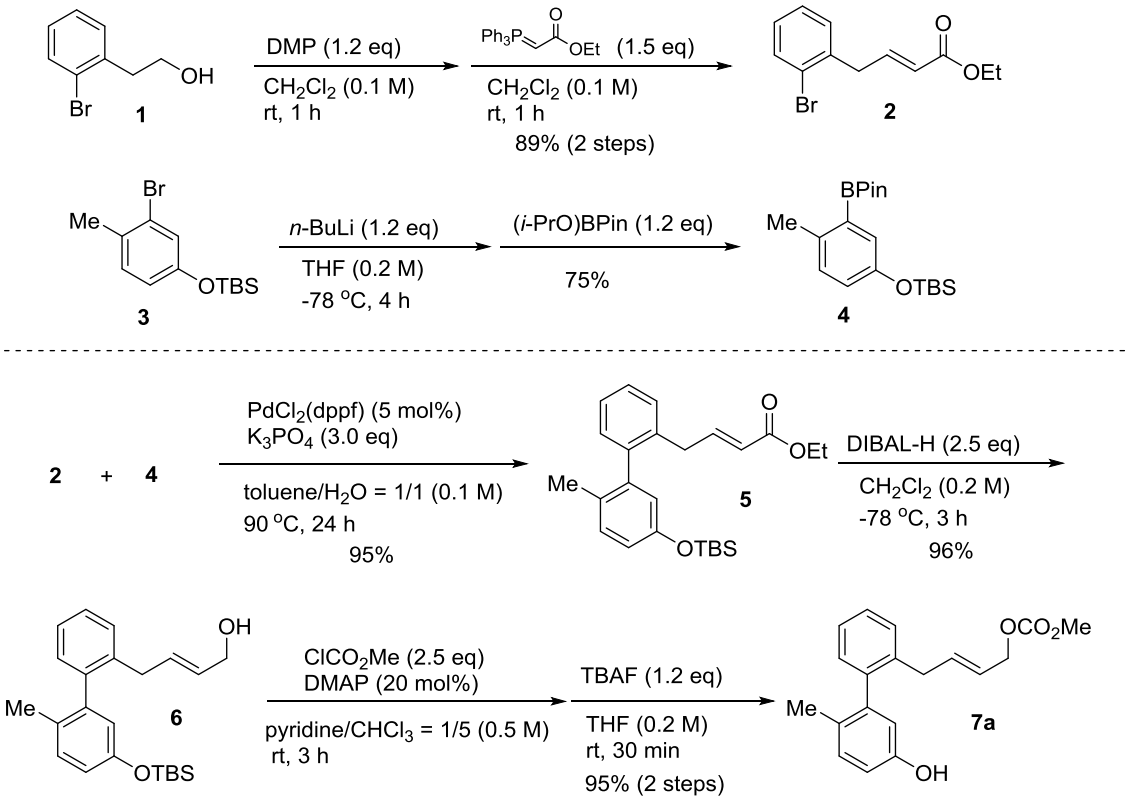


先述の通り、本研究は医薬有用分子として期待される複雑縮環分子の効率的創出が見込めるため、有機化学のみならず創薬化学的な側面からも魅力的である。以上の背景のもと、フェノール類の触媒的分子内 Friedel–Crafts 型アリル位アルキル化反応を利用した 9,10–ジヒドロフェナントレン類の新規不斉合成法の開発研究に着手した。

第四節　反応条件の最適化

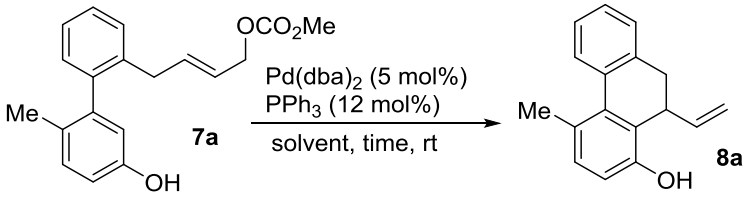
7a をモデル基質として反応条件の最適化を行うこととし、基質を以下のように調製した。初めに市販のアルコール体 **1** に Dess–Martin 酸化を行い、続く Wittig 反応により上部ユニット **2** を合成した。下部ユニット **4** は既知化合物 **3** をリチオ化し、ボロン酸エステルを導入することで合成した。得られた両ユニット **2**、**4** を $PdCl_2$(dppf)触媒存在下、鈴木―宮浦クロスカップリング [11] を行うことでビフェニル体 **5** とした後、エステル部位の DIBAL–H 還元、続くアルコールのカーボネート保護、最後に TBS 基の脱保護を経てモデル基質 **7a** を得た。

Scheme 1-8. Substrate synthesis



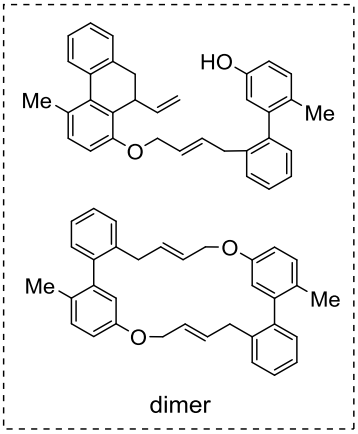
合成した基質 **7a** に対し、スピロ環合成反応にて確立された最適条件を適用したところ、目的環化体 **8a** の収率は僅か 12%に留まり、分子間 *O*-アリル化反応に由来する数種の多量体副生成物が確認された(Table 1-1. entry 1)。副反応を抑えるべく各種溶媒について検討を行ったが、収率の改善には至らなかった。

Table 1-1. Initial trial



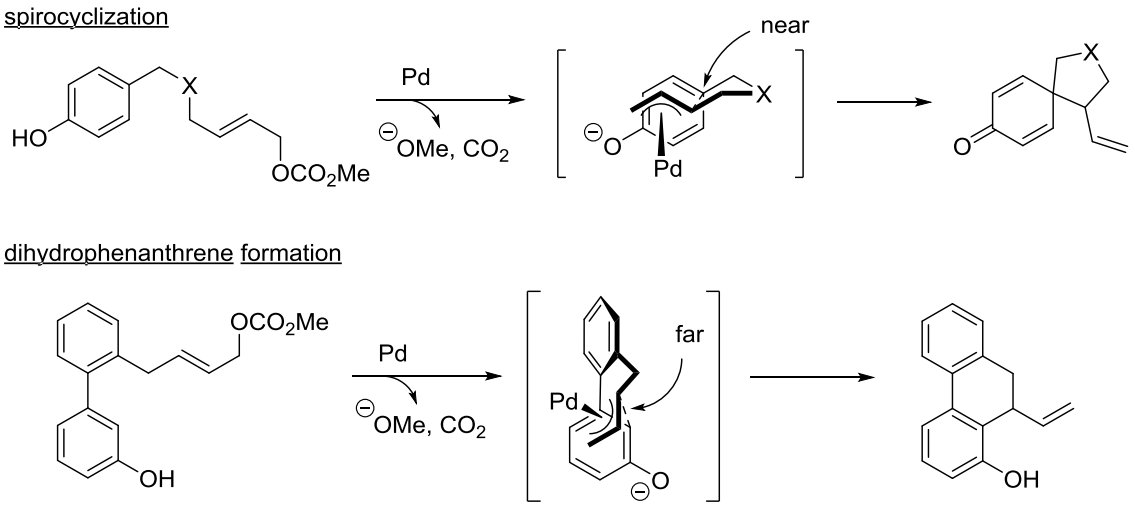
entry	solvent	time (h)	yield [a] (%)
1	CH_2Cl_2	5	12
2	THF	3	trace
3	toluene	5	11
4	CH_3CN	16	trace

[a] Isolated yield.



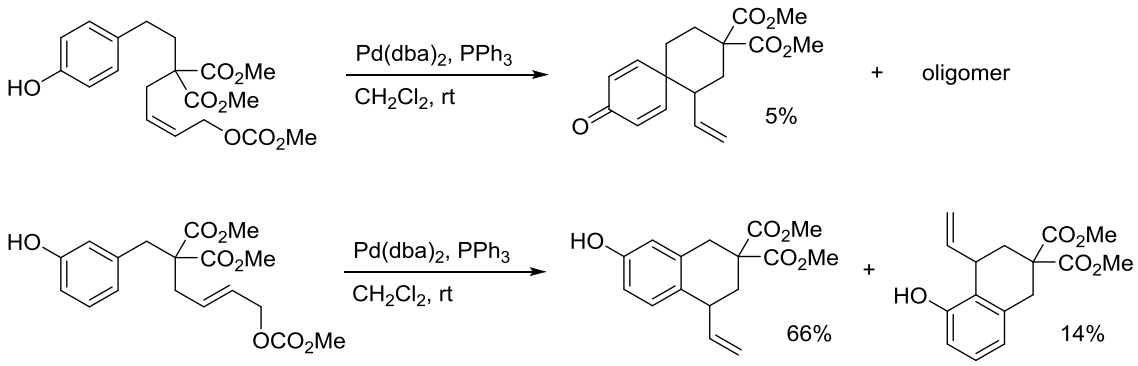
本反応は基質のフェノール性水酸基が反応系中において発生したメトキシドアニオンによって脱プロトン化を受け、生じたフェノキシドアニオンが活性種として働くと考えられている[7]。この知見を踏まえ、フェニルフェノール型の基質において反応性が低下した原因を以下のように考察した。先のスピロ環合成は五員環形成反応であった上に架橋部位の構造も柔軟性に富んでいたため、遷移状態においてπ-アリルパラジウムカチオンとフェノキシドアニオンが近づきやすく、容易に相互作用し得ると予想される。一方で今回の反応は六員環形成反応である上に架橋部位の構造が非常に強直であるため、反応点が近づきにくく分子間反応が競合したものと思われる。

Figure 1-2. Transition state of the intramolecular Friedel-Crafts allylic alkylation



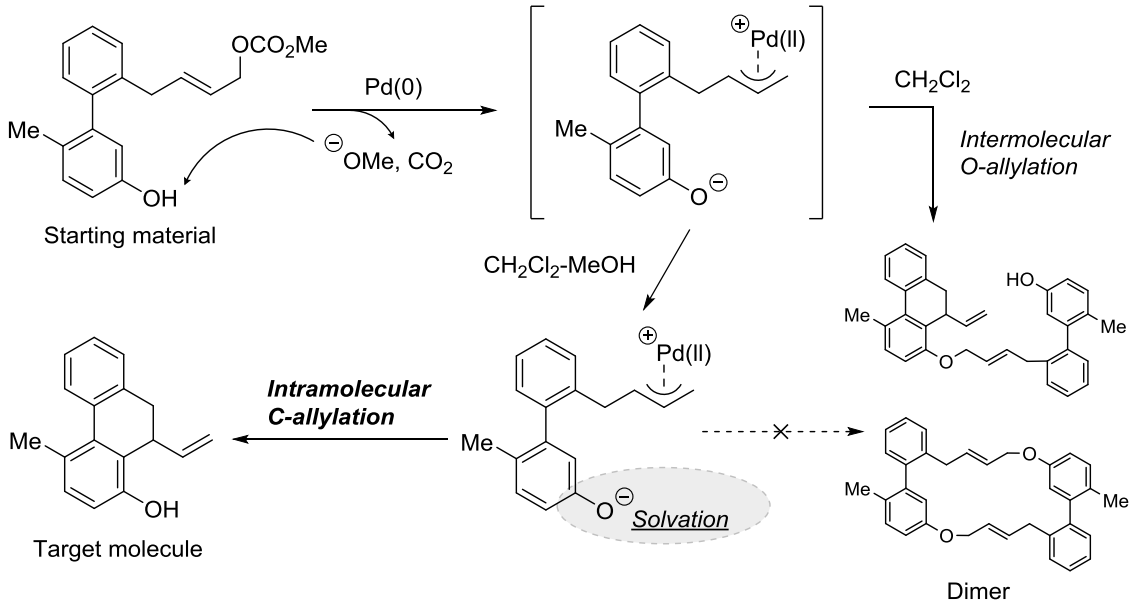
実際スピロ環化反応においても、一炭素増炭された基質を用いて六員環形成を試みた場合収率が著しく低下する。一方で、メタ置換体による環化も架橋部位が sp3 炭素であれば反応は収率良く進行する。

Scheme 1-9. Pd-catalyzed intramolecular Friedel- Crafts allylic alkylation of phenols



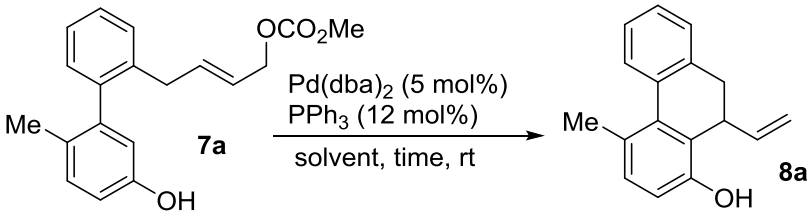
いずれにしても、競合する分子間反応を抑えなければ収率の改善は見込めない。そこで予想される反応機構を吟味し、次の仮説を立てた。低収率の原因である多量体は、基質の酸化的付加により生じた双性イオン中間体のフェノキシドアニオンが、もう一当量の基質と反応して得られたものと予想される。そこで、反応系中にプロトン性溶媒を混在させることで本中間体を溶媒和させれば、*O*-アルキル化が抑えられるのではないかと予想した。そうすれば相対的に分子内 *C*-アルキル化が優先され、結果として収率の改善につながると期待した。

Figure 1-3. Strategy to avoid the intermolecular *O*-allylation



そこで実際に溶媒を MeOH との混合溶媒として反応を行ったところ、狙い通り副反応は抑えられ、収率は劇的に改善された (Table 1-1. entry 1) 。更に溶媒種や比率に関して綿密な検討を行った結果、CH_2Cl_2/MeOH = 4/1 の条件において環化体を収率 72%にて得ることに成功した(entry 2)。なお、溶媒比率やプロトン源の種類により招かれる収率の低下は、溶媒和の度合いや分子内環化の反応性に起因すると思われる。つまり、本反応は適度な溶媒和が重要であると示唆される。

Table 1-2. Solvent effect



entry	solvent	time (h)	yield [a] (%)
1	THF/MeOH = 4/1	6	63
2	CH_2Cl_2/MeOH = 4/1	16	71
3	CH_2Cl_2/MeOH = 1/1	16	12
4	CH_2Cl_2/MeOH = 9/1	16	46
5	CH_2Cl_2/*t*-BuOH = 4/1	16	30

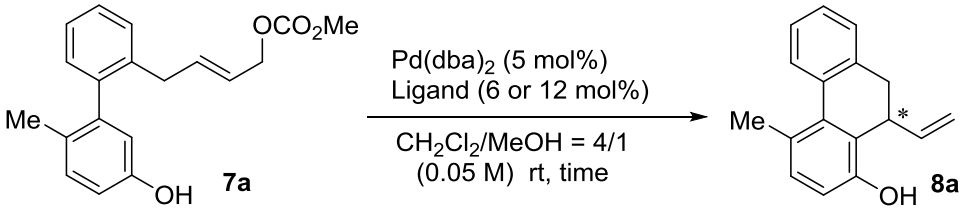
[a] Isolated yield.

以上の検討結果から、CH_2Cl_2/MeOH = 4/1 を最適溶媒として用いることとした。

第五節　触媒的不斉反応への展開

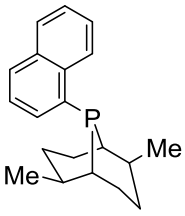
反応の不斉化を目指し、キラル配位子のスクリーニングを行った。まず単座配位子として 9-NapBN[12]、Monophos[13]、MOP[14] 配位子を試したものの、いずれの配位子を用いた場合もほとんど選択性を示さず、反応性も不十分であった(entry 1–3)。続いて、二座配位子 PHOX[15]、Trost 配位子について検討を行ったところ、DACH-Trost ligand を用いた際に中程度ながら選択性が誘起された(entry 5)。更なる検討の結果、ANDEN-Trost ligand を用いることで 97%収率、91% ee にて **8a** を得ることに成功した(entry 7)[16]。なお、その際得られた化合物の立体化学は、DACH-Trost ligand を用いた際とは逆のものであった。

Table 1-3. Screening of chiral ligands

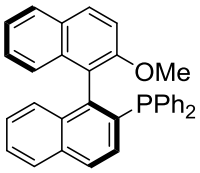


entry	ligand	time (h)	yield [a] (%)	ee [b] (%)
1	(*S*)-9-NapBN (12)	10	trace	-
2	(*R*)-Monophos (12)	6	56	-4
3	(*S*)-(–)-MOP (12)	16	62	-7
4	(*S*)-*i*-Pr-PHOX (6)	16	trace	-
5	(*R,R*)-DACH-Ph-Trost ligand (6)	16	66	-65
6	(*R,R*)-DACH-nap-Trost ligand (6)	16	88	-10
7	(*R,R*)-ANDEN-nap-Trost ligand (6)	10	97	91

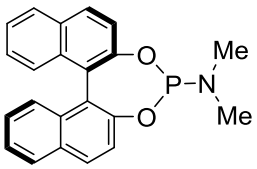
[a] Isolated yield. [b] Determined by chiral HPLC analysis.



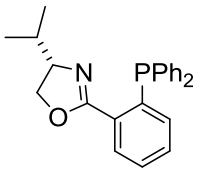
(S)-9-NapBN



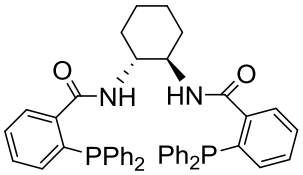
(*S*)-(–)-MOP



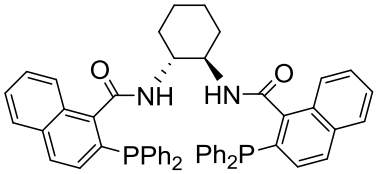
(*R*)-MONOPHOS



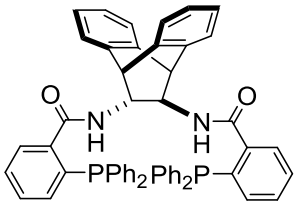
(*S*)-*i*-Pr-PHOX



(*R,R*)-DACH-Ph-Trost ligand



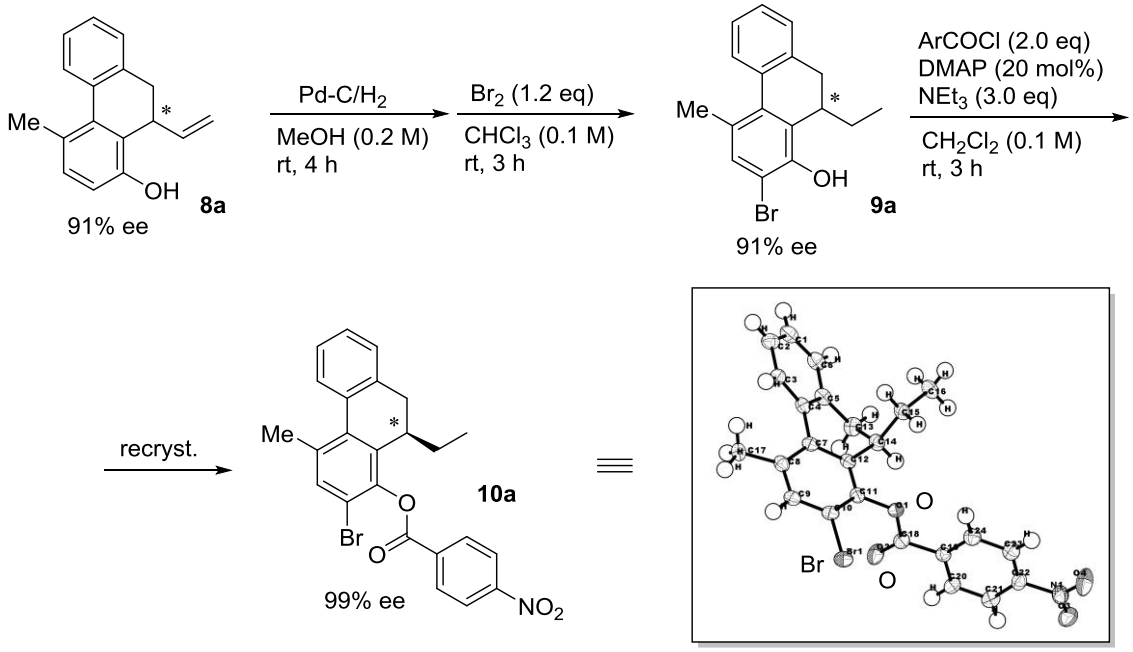
(*R,R*)-DACH-nap-Trost ligand



(*R,R*)-ANDEN-Ph-Trost ligand

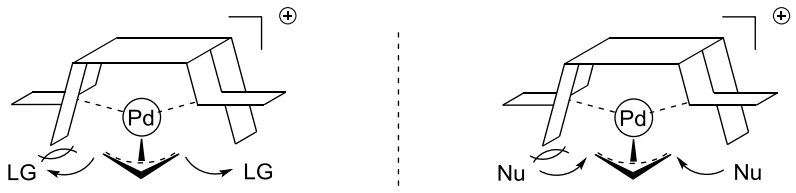
得られたキラルな環化体 **8a** を誘導体化し、X 線結晶構造解析にてその絶対立体配置を決定した。実際の合成を以下に示す。まず側鎖の二重結合を水素化により還元し、続いて芳香環に臭素を導入することで **9a** へと導き、最後にフェノール性水酸基を *p*-NO_2Bz 基で保護することによって白色固体 **10a** を得た。得られた **10a** を再結晶により光学的に純粋なものとし X 線結晶構造解析を行った結果、その立体化学は *R* 体であったことから **8a** は *S* 体であると決定した [17]。

Scheme 1-10. Determination of the absolute configuration



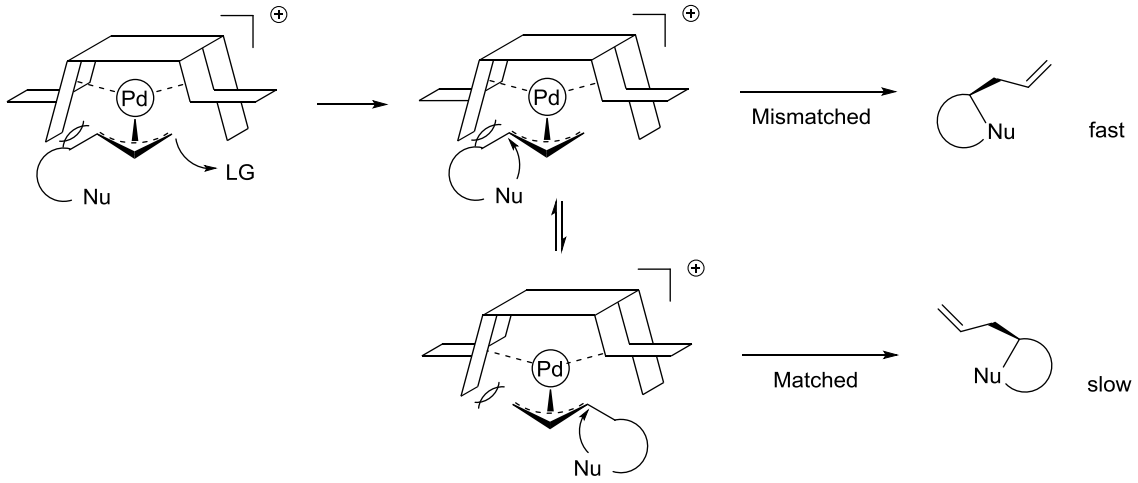
DACH 型と ANDEN 型の配位子を用いた場合にそれぞれ異なる選択性を与えた理由に関しては、残念ながら詳細の解明には至っていない。考えられる機構として、Trost ligand による不斉アリル位アルキル化反応のメカニズム解析に用いられる分子モデルを応用した考察を次に記載する [18]。不斉アリル位アルキル化反応は、メソ体でもプロキラル体でもない一般的なアリル源を基質として使用した場合、酸化的付加段階と求核付加段階の２点において配位子が関与する。

Scheme 1-11. The possible modes of enantio selection in the asymmetric allylic alkylation using the Trost ligands



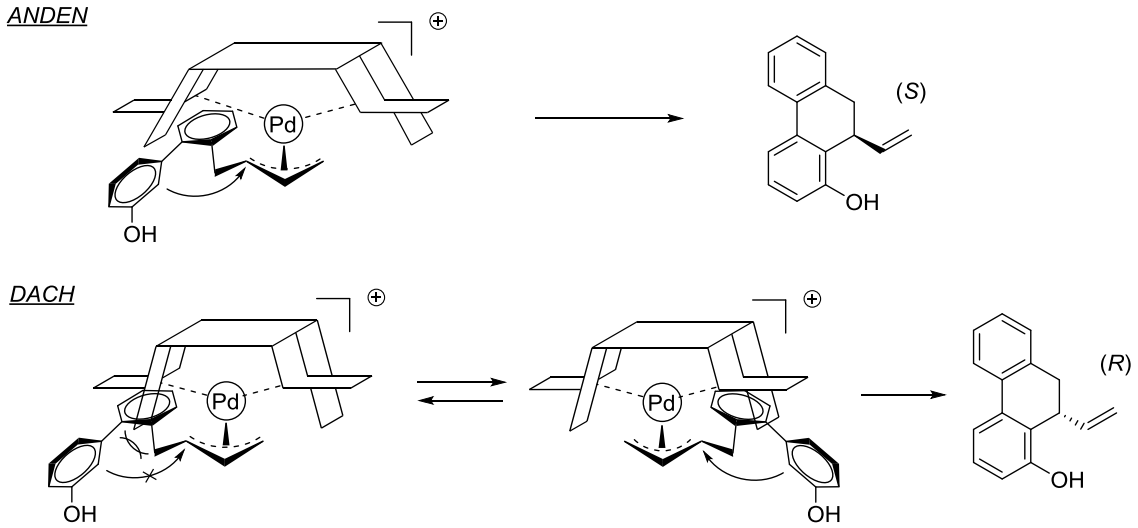
分子内反応の場合は脱離基と求核部位が同一分子内に存在するため、この二つの段階を考慮した複雑な反応予測をしなければならない。仮に立体障害による影響が軽微であり求核付加が迅速に進む場合、生成物の立体化学は一つ目の酸化的付加段階で決定する。一方、求核付加が遅い場合は、σ錯体を経由したπ–アリル錯体の異性化が優先し、より求核部位が近づきやすい配置から反応は進行する。

Scheme 1-12. Intramolecular asymmetric allylic alkylation



ANDEN 型配位子は DACH 型と比べて配位挟角が広いことが知られている。そのため、比較的コンパクトな構造をしている基質 **7a** は、ANDEN 型配位子の作る空間に上手く入り込めたことで求核攻撃がスムーズに進行したと予想できる。反対に DACH 型配位子の場合では、求核攻撃が配位子により阻害され異性化が優先したと考えられる。その結果、各配位子を用いた際にそれぞれ逆の立体化学を有する環化体 **8a** が得られたものと思われる。

Scheme 1-13. Intramolecular asymmetric allylic alkylation

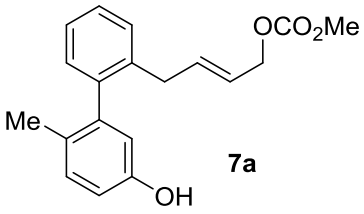
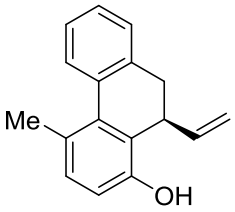
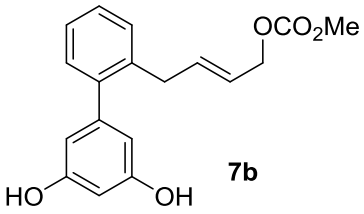
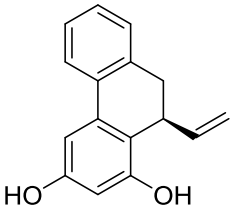
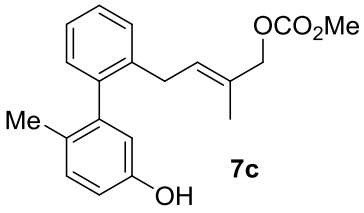
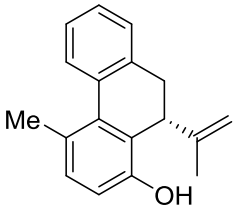
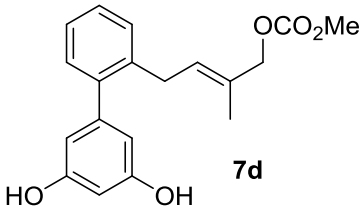
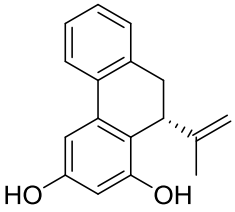
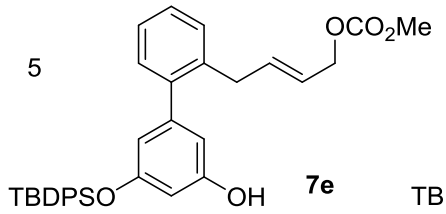
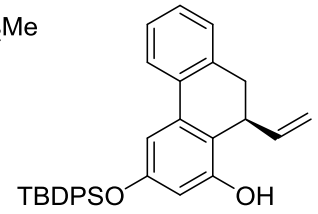


しかし、本考察は反応がπ-アリル錯体を経由して進行しているという仮定に基づくものであり、現実にどういったメカニズムによるものかを正確に把握することは難しい。実際、反応条件次第では配位子が二座ではなく単座で機能し、σ-アリル錯体由来で反応が進行する可能性を指摘している論文も存在する[18]。

第六節　基質一般性の検討

得られた最適条件の下、基質適応範囲について検討を行った(Table 1-4)。側鎖を三置換オレフィンとした基質では、DACH-Trost ligand を用いて熱をかけることで側鎖にイソプロペニル基を有する環化体 **8b** を高収率、高立体選択的に得ることに成功した。なお、この際得られた **8b** の旋光度は、**8a** とは逆の値を示した(entry 1,2)。

Table 1-4 (1). Scope and limitations

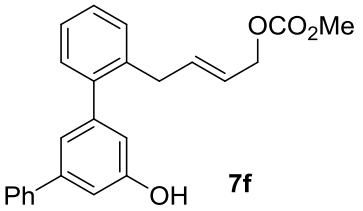
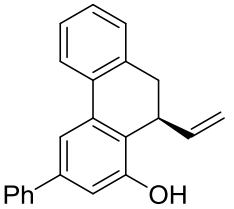
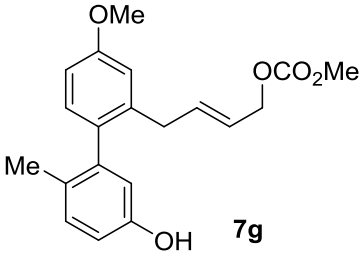
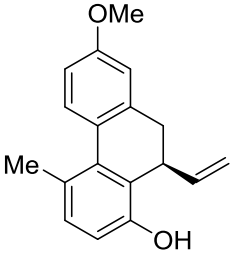
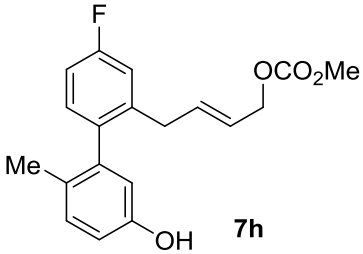
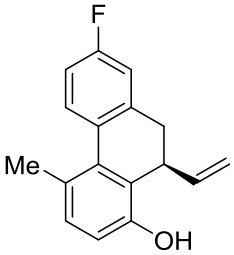
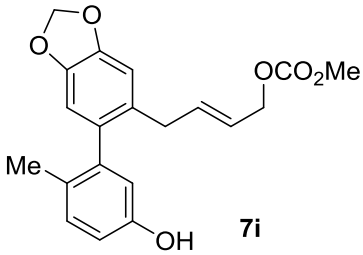
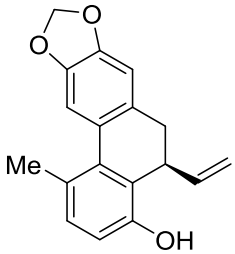
entry	substrate	product	results [a]
1	 **7a**		(*S*)-(+)-**8a** 6 h, rt 97% yield 91% ee (*R,R*)-ANDEN-Trost ligand (DACH: -65% ee)
2	 **7b**		(+)-**8b** 6 h, rt 99% yield 90% ee (*R,R*)-ANDEN-Trost ligand (DACH: -70% ee)
3	 **7c**		(–)-**8c** 16 h, 40 °C 96% yield 93% ee (*R,R*)-DACH-Trost ligand
4	 **7d**		(–)-**8d** 16 h, rt 90% yield 91% ee (*R,R*)-DACH-Trost ligand (ANDEN: 39% ee)
5	 **7e**		(+)-**8e** 16 h, rt 85% yield 92% ee (*R,R*)-ANDEN-Trost ligand

Reaction conditions: $Pd(dba)_2$ (5 mol %), ligand (6 mol %), CH_2Cl_2/MeOH = 4/1 (0.05 M)
[a] Isolated yield. Enantiometric excesses were determined by chiral HPLC analysis.

下部ユニットの置換様式に関しても検討を行った。レゾルシノール型の基質においても反応は問題なく進行し、側鎖を三置換オレフィンとした場合にも良好な結果を与えた (entry 3,4) 。さらに、求核部位の構造を非対称なフェノールとした場合においても、ある程度の立体障害があれば位置選択的に反応は進行することがわかった(entry 5,6)。

上部ユニットの構造についても各種検討を行ったところ、電子求引性、供与性の両置換基やメチレンジオキシ基の導入された基質において、反応は問題なく進行した(entry 7–9)。

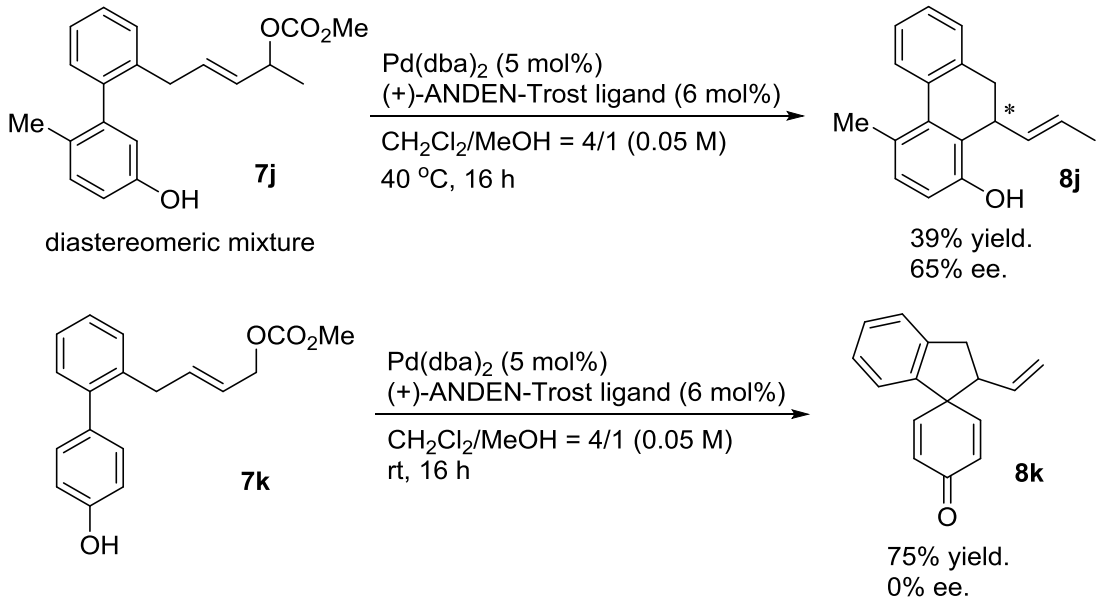
Table 1-4 (2). Scope and limitations

entry	substrate	product	results [a]
6	 **7f**		(+)-**8f** 16 h, rt 83% yield 94% ee (*R,R*)-ANDEN-Trost ligand
7	 **7g**		(+)-**8g** 16 h, rt 96% yield 94% ee (*R,R*)-ANDEN-Trost ligand
8	 **7h**		(+)-**8h** 16 h, rt 83% yield 94% ee (*R,R*)-ANDEN-Trost ligand
9	 **7i**		(+)-**8i** 16 h, rt 82% yield 87% ee (*R,R*)-ANDEN-Trost ligand

Reaction conditions: $Pd(dba)_2$ (5 mol %), ligand (6 mol %), CH_2Cl_2/MeOH = 4/1 (0.05 M)
[a] Isolated yield. Enantiometric excesses were determined by chiral HPLC analysis.

一方で、生成物の側鎖に直鎖状の置換基が導入されるような基質においては、反応性の低下と二量体の生成が観測された上、立体選択性に関しても不十分なものであった。また、パラ置換型フェノール誘導体を基質として用いた場合、スピロ環化体を得ることには成功したものの、立体選択性は全く誘起されなかった。

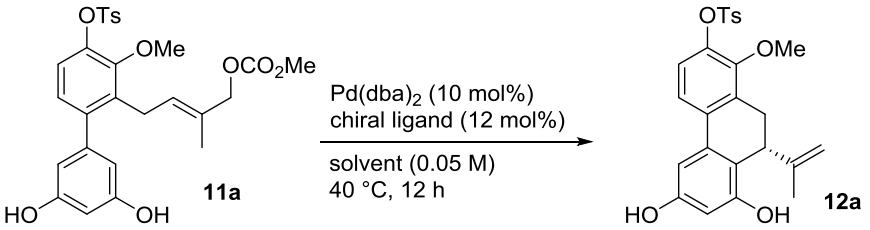
Scheme 1-14. Scope and limitations.



第七節　Cedrelin A、Paralycolin B の全合成

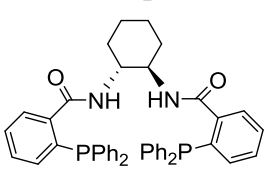
ジヒドロフェナントレン類の効率合成法開発に成功したため、天然物全合成への応用を目指すこととした。まず Cedrelin A[9a] を合成ターゲットと定め、基質 **11a** を合成し検討を開始した。しかし、最適条件を用いて反応を行ったところ、光学収率の著しい低下が確認された(Table 1-5. entry 1)。そこで、各種溶媒や添加剤等について再度検討を行ったところ、THF/MeOH 溶媒中酢酸カリウムを添加して反応を行うことで ee が改善されることを見出した(entry 8)。その値は依然として中程度ではあったものの、これ以上の改善は見込めなかったため本条件を採用し、先の検討へ移ることとした。なお、触媒量を減らすと反応は完結せず、一部原料が残った(entry 10)。

Table 1-5. Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of **11a**

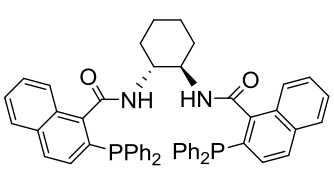


entry	solvent	chiral ligand	additive	yield (%)[a]	ee (%)[b]
1	CH_2Cl_2/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	-	94	29
2	CH_3CN/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	-	33	36
3	toluene/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	-	31	38
4	THF/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	-	88	60
5	THF/MeOH = 4/1	(*R,R*)-DACH-nap-Trost ligand	-	n.r.	-
6	THF/MeOH = 4/1	(*R,R*)-ANDEN-Ph-Trost ligand	-	n.r	-
7	THF/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	LiOAc	83	38
8	THF/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	KOAc	98 (94)[c]	66
9	THF/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	$Mg(OAc)_2$	75	65
10[d]	THF/MeOH = 4/1	(*R,R*)-DACH-Ph-Trost ligand	KOAc	45	60

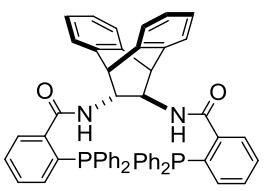
[a] Determind by ^{1}H-NMR analysis of the crude mixture.
[b] Determined by chiral HPLC analysis.
[c] Isolated yield.
[d] 5 mol% of $Pd(dba)_2$ and 6 mol% of ligand were used.



(*R,R*)-DACH-Ph-Trost ligand



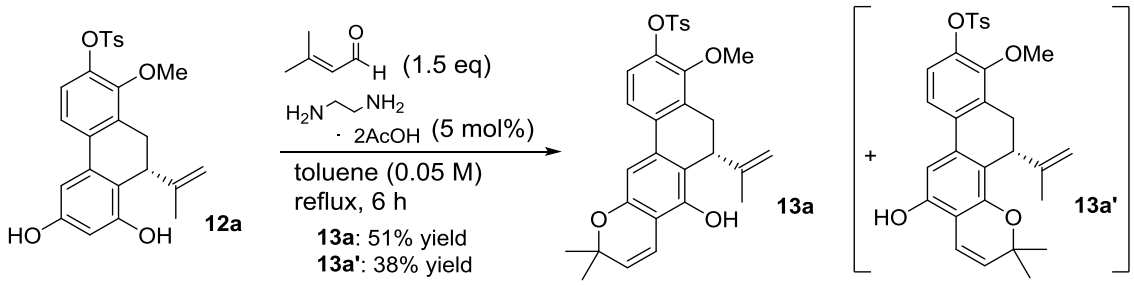
(*R,R*)-DACH-nap-Trost ligand



(*R,R*)-ANDEN-Ph-Trost ligand

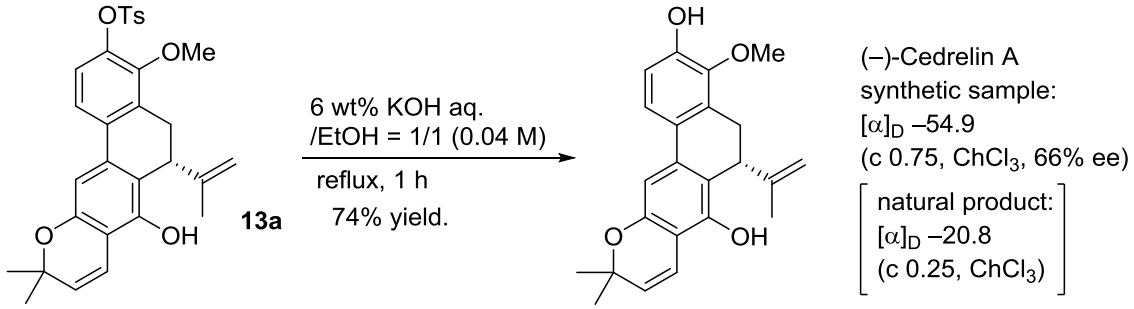
続いて Lee らの条件を参考にクロメン環形成を行った[19]。すなわち、エチレンジアミン二酢酸存在下、環化体 **12a** に対し 3,3-ジメチルアクロレインを作用させることで、天然物の母骨格となる四環性化合物 **13a** を合成した。その際、位置異性体 **13a'** も同時に得られたが。シリカゲルカラムにより容易に分離可能であった。

Scheme 1-14. Formation of the chromene ring



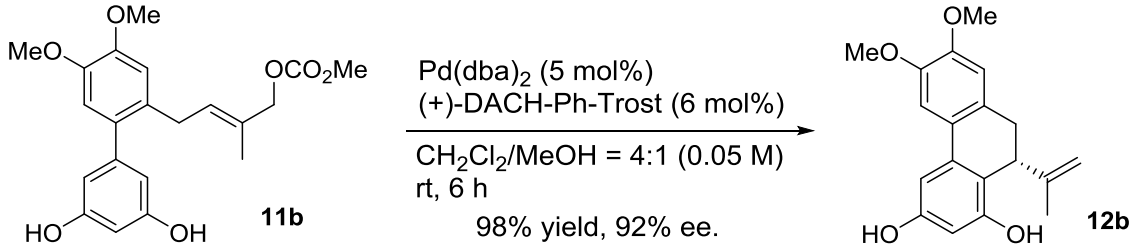
最後に単離した **13a** を、塩基性条件下 Ts 基の脱保護を行うことで天然物(–)-Cedrelin A の新規不斉全合成を達成した。合成品の各種スペクトルデータは文献値と良い一致を示し、旋光度と CD スペクトルから天然と同じ一体であることも明らかにした。なお、合成の各段階において、中間体や誘導体の結晶化による ee の改善も試みたが、達成できなかった。

Scheme 1-15. Total synthesis of (–)-cedrelin A



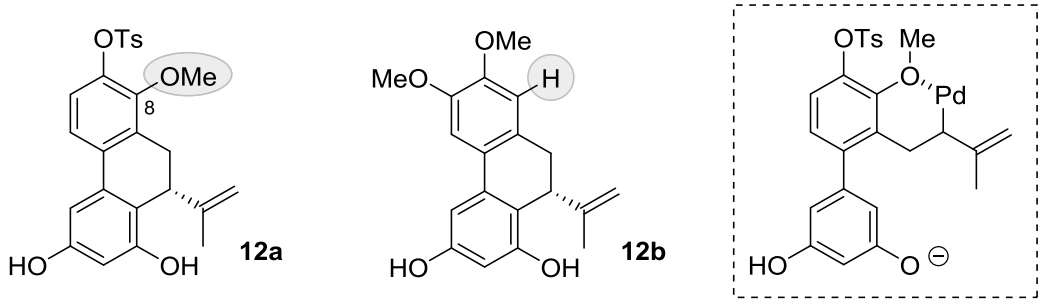
続いて Cedrelin A の構造類縁体である Paralycolin B の全合成を目指し検討を行った。その結果、フェノール **11b** を基質とした分子内 Friedel–Crafts 型アリル位アルキル化反応は最適条件非常にスムーズに進行し、高い立体選択性にてジヒドロフェナントレン **12b** を与えることがかった。

Scheme 1-16. Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of **11b**



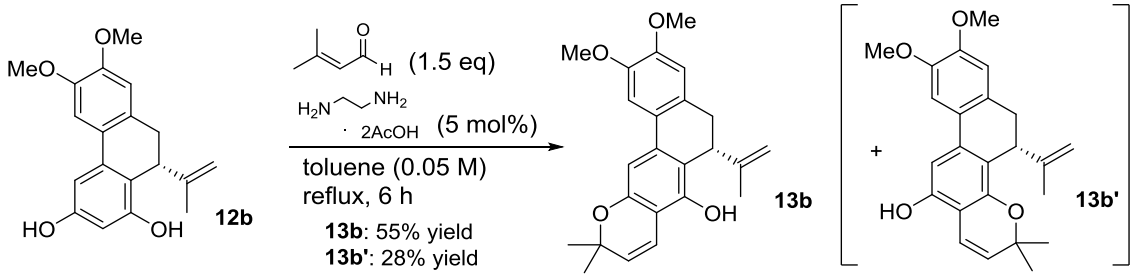
以上の結果より、本反応は 8 位置換基の存在が反応性、選択性に大きく影響を与えることが明らかとなった。原因について、単純な基質と配位子の立体障害によるものか、或いはエーテル酸素原子が Pd 触媒に配位することで触媒系を阻害したのではないかと推測しているが、詳細はわかっていない。

Figure 1-4. Substituent effect of the methoxy group on the 8 position



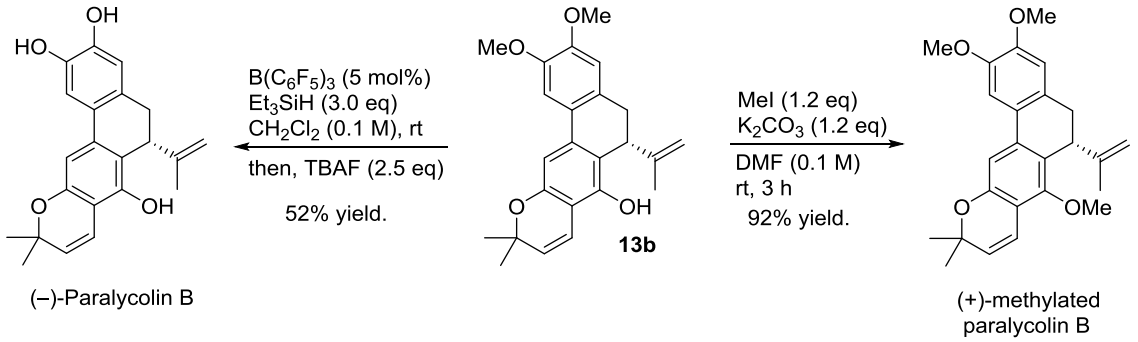
いずれにしても光学純度の高い **12b** が得られたため、続いて先と同様の手法にてクロメン環形成を行った。なお、この際も反対側の水酸基に環化が進行した **13b'**が **13b** と同時に得られたが、シリカゲルカラムにより分離可能であった。

Scheme 1-17. Formation of the chromene ring



最後に、各種官能基変換により Paralycolin B の全合成を行った。実際の単離文献には、すべての水酸基にメチル化が施された methylated Paralycolin B の化合物データが記載されていたため、まずそちらの合成を行った。すなわち、単離した **13b** の 1 位水酸基をヨードメタンによりメチル化することで methylated Paralycolin B の全合成を達成した[20]。また、天然物である Paralycolin B 自体も、二つのメトキシ基を $B(C_6F_5)_3$ 触媒によりシロキシ基へと変換し、続く TBAF による脱保護を行うことで合成した。しかしこの際、イソプロペニル基の還元が進行した化合物も、単離できない副生成物として同時に与えた。

Scheme 1-18. Total synthesis of Paralycolin B

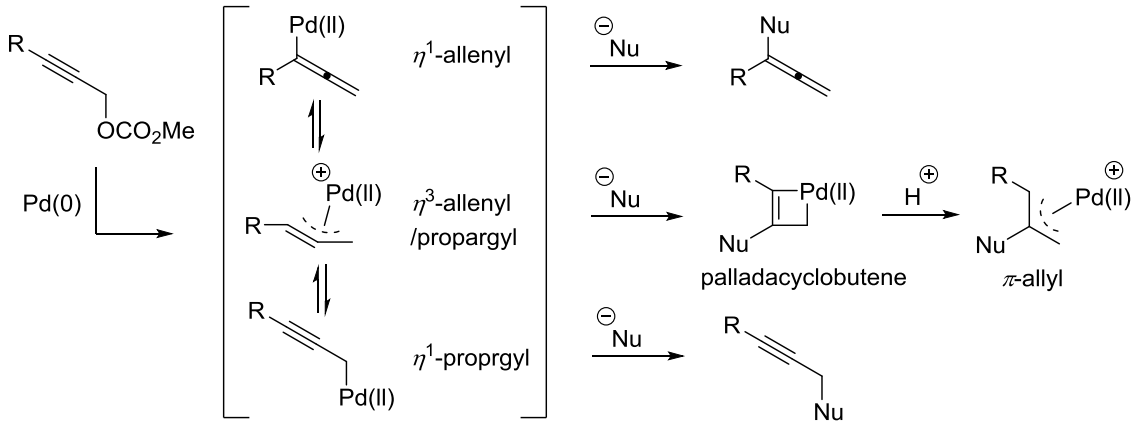


第二章　Friedel–Crafts 型 C–H カップリング―アミノ化連続反応による新規 3,4 位縮環型三環性インドール類合成法の開発

第一節　背景

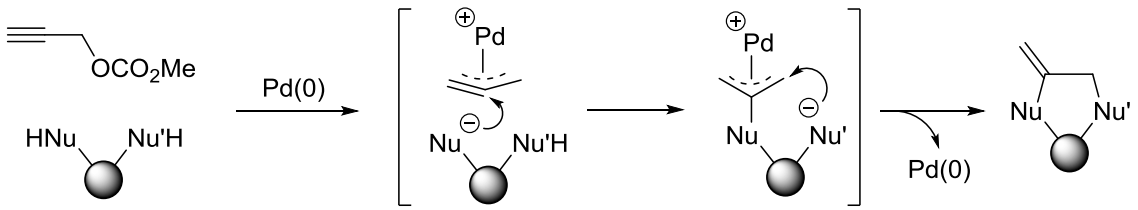
プロパルギルカーボネートに対して Pd 触媒を作用させると、η^1-及びη^3-アレニル/プロパルギル錯体の平衡混合物を形成することが知られている[21]。このカチオン性η^3–アレニル/プロパルギル錯体は、アレン様の性質を有しながらも直線よりやや歪んだ特異な構造をとっているため、中心炭素へ求核付加を受ける[22]。また、後に生成するパラダシクロブテン中間体は、プロトン化によりπ–アリルパラジウム錯体へと変換される。

Scheme 2-1. Reaction mechanism of allenyl / propargyl palladium complexes



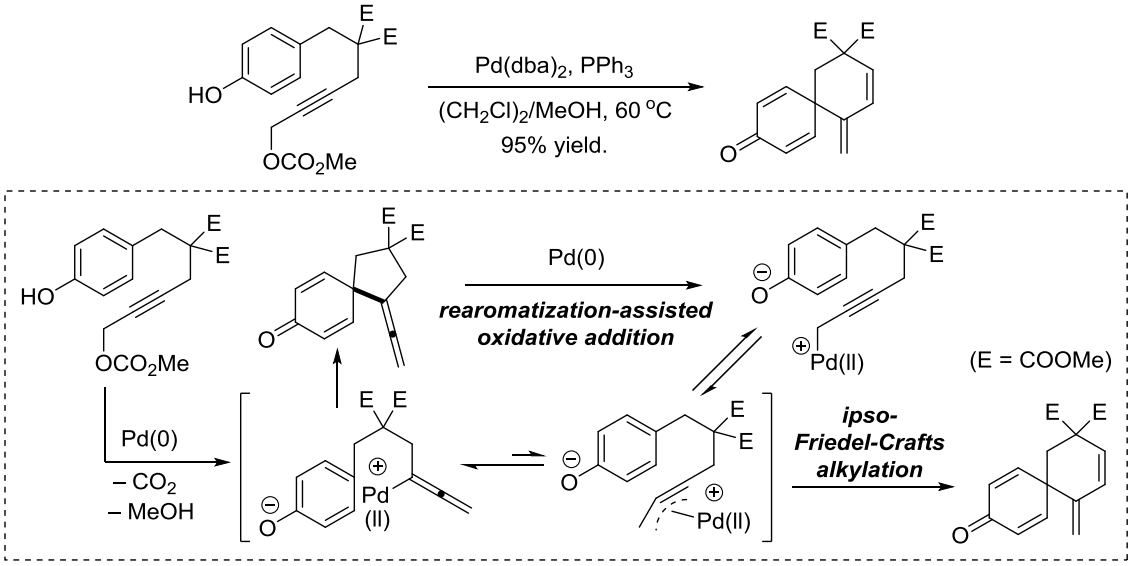
つまり、η^3-アレニル/プロパルギル錯体は中心炭素と末端炭素の二点が電子受容体として機能するため、それぞれの部位が求核剤と反応することで二点同時結合形成が可能となる。いわゆるカスケード反応を触媒的に可能とする魅力的な化学種であるため、本錯体に関する研究は近年特に盛んとなっている[23]。しかし一方で、基質や求核剤の種類によってはη^1–アレニル錯体やプロパルギル錯体への求核付加が優先され、アレン型生成物やプロパルギル位置換体を主として与えることがある。この位置選択性の制御がしばしば問題となるため、本反応の実用例は未だ限定的である。

Scheme 2-2. Palladium-catalyzed cascade reaction of propargyl esters with bis-nucleophiles



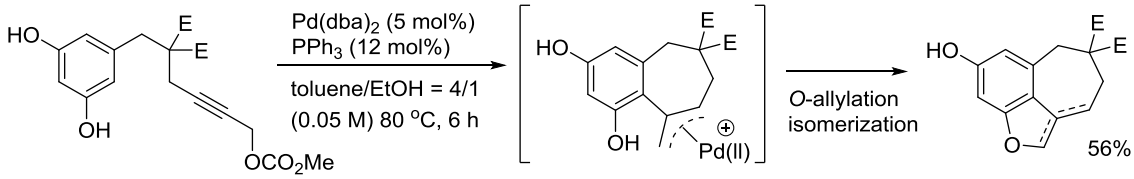
一方で我々は近年、側鎖にプロパルギルカーボネート部位を持つパラ置換型フェノール誘導体に Pd 触媒を作用させることで、η^3-アレニル/プロパルギル錯体に対して分子内 *ipso*–Friedel–Crafts 型の付加反応が進行することを見出した[24,25]。発生したπ–アリルパラジウム錯体はその後、β水素脱離を受けスピロ[5, 5]シクロヘキサジエノン類へと変換される。なお、本反応は速度論的に生成するアレン型中間体の、C–C 結合の開裂を伴う Pd 触媒への酸化的付加を経由していることが反応機構解析から明らかとなっている。すなわち、本反応系ではアレン型生成物とη^3–アレニル/プロパルギル錯体との間に可逆反応を成立させることで位置選択性を制御している。

Scheme 2-3. Pd-catalyzed intramolecular *ipso*-Friedel–Crafts alkylation of phenols



また、メタ置換型レゾルシノール誘導体を基質とした場合には Friedel–Crafts 型の付加反応に続く分子内 *O*-アリル化が進行し、ベンゾフラン誘導体を中程度の収率で与えることも見出している。

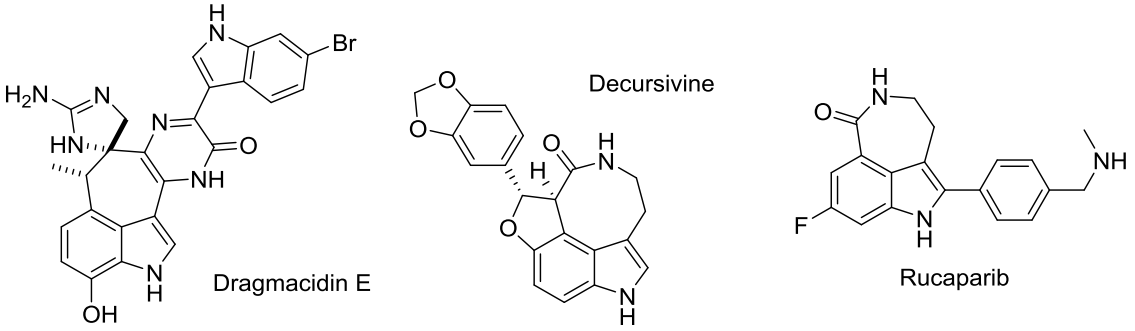
Scheme 2-4. Pd-catalyzed intramolecular Friedel–Crafts alkylation-*O*-allylation cascade



第二節　研究目的

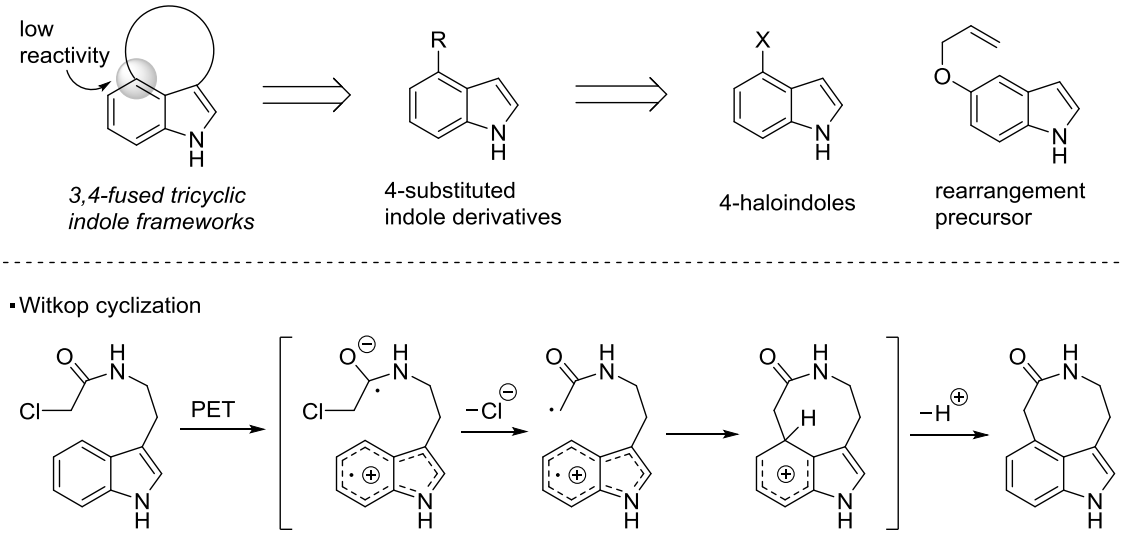
インドールの 3,4 位から中員環が縮環した化合物群は生物活性天然物や医薬品に多く見られる共通構造であり、そのユニークな構造と魅力的な生物活性から、近年特に注目を集めている。

Figure 2-1. Bioactive compounds with a 3,4-fused tricyclic indole skelton



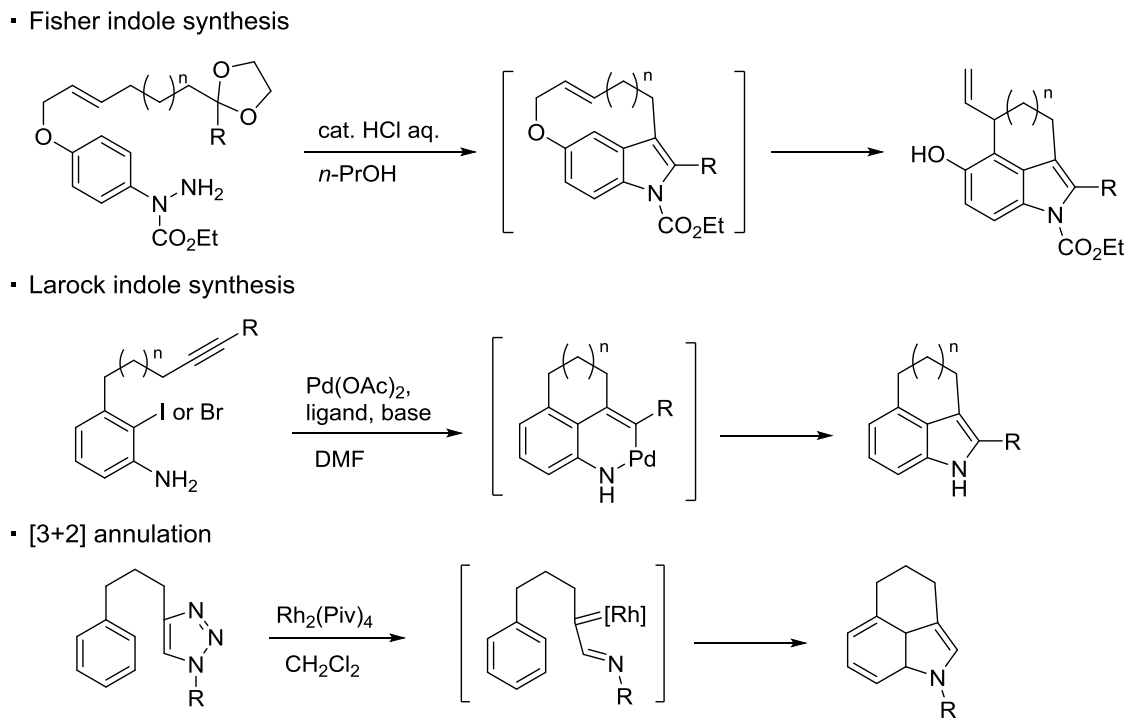
しかし、本骨格の合成にはインドール 4 位の修飾が必須であるが、この位置は電子密度が低く反応性に乏しいことが知られている。つまり直接的な修飾が困難であり、4 位に予め置換基の導入された基質を用いる必要がある [26]。そのため、高価な 4-ハロインドールや転位反応前駆体を原料とした段階的な合成法がこれまでの主流であった [27,28]。また、直接的な合成法として光誘起電子移動（photoinduced electron transfer; PET）による Witkop 環化が古くから知られているが、本反応も収率や基質適応範囲に課題を残している [29]。

Scheme 2-5. Synthesis of 3,4-fused indoles from indole derivatives



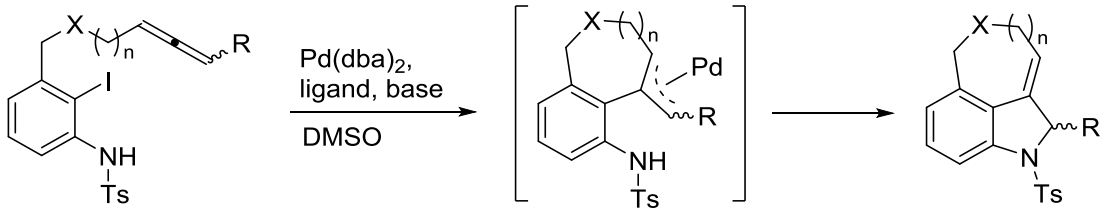
一方、最近ではアニリンやベンゼン誘導体を原料とした新たな 3,4 位縮環型インドール類合成法の開発に注目が集まっている。その代表例を以下に示す。2012 年、Cho らは分子内 Fischer インドール合成に続く分子内 Claisen 転位により本骨格を合成することに成功した[30]。また、2013 年には Boger らと Jia らによって分子内 Larock インドール合成を応用した効率合成法がそれぞれ独立に開発された[31]。さらに 2014 年、ロジウムイミノカルベノイドの反応性を応用した [3+2]環化による合成法が村上らによって報告された[32]。

Scheme 2-6. Efficient synthesis of 3,4-fused tricyclic indole frameworks



当研究室でも最近、アレン側鎖を有するヨードアニリン誘導体を基質とした分子内 Heck 挿入―アリル位アミノ化連続環化により、3,4 位縮環型インドリン類の効率合成に成功している。得られた環化体は酸により容易にインドール体へと変換できることも明らかにしている[33]。

Scheme 2-7. Synthesis of 3,4-fused indolines; intramolecular Heck insertion-allylic amination



しかし、これらの反応は

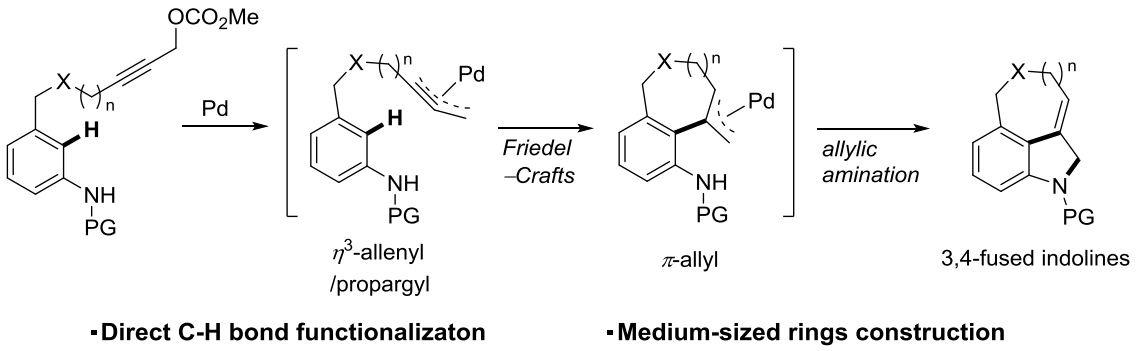
① 芳香環上に導入困難な脱離基（ハロゲン等）を必要とするため、基質の調製が煩雑

② 幅広い縮環サイズや様々な置換パターンへの適用が困難

といった課題を抱えており、より汎用性の高い反応の開発が求められる[34]。

我々が以前開発したη^3-アレニル/プロパルギル錯体に対する分子内 Friedel–Crafts 型付加反応[24]は、求核部位をメタ置換型アニリンとすれば、上と同様の 3,4 位縮環型インドリン類を与えることが予想できる。冒頭でも述べたように、Friedel–Crafts 型反応は形式上芳香環 C–H 結合を直接的に修飾できるため、芳香環上への多彩な置換基導入をより簡略化できる。また、η^3-アレニル/プロパルギル錯体への分子内環化反応は中員環形成への応用実績も存在する。これらの見識に鑑みれば、本反応は上述した課題を一掃できる強力な 3,4 位縮環型インドール類の新規合成法として期待が持たれる。

Scheme 2-8. Reaction design

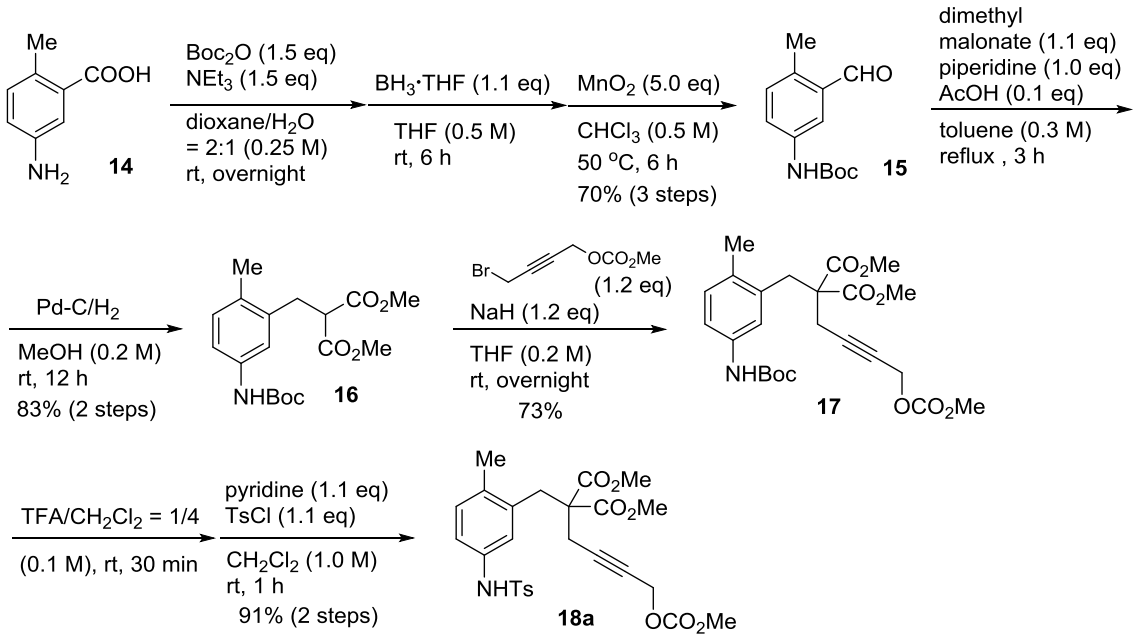


以上の背景の下、アレニル/プロパルギル錯体の反応性を応用した、分子内 Friedel–Crafts 型アルキル化反応による新規 3,4 位縮環型三環性インドール類合成法の開発研究に着手した。

第三節　Pd 触媒を用いた検討

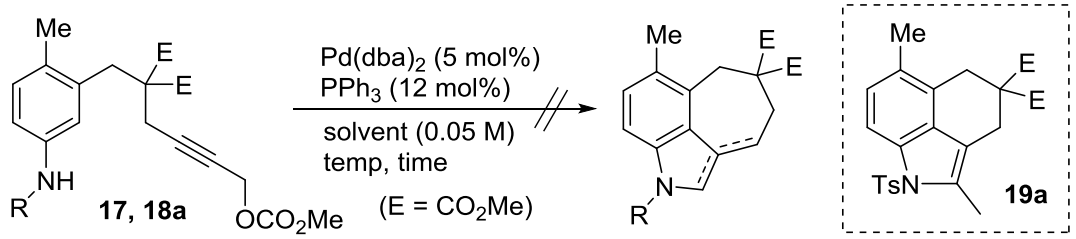
設計したアニリン誘導体を以下の合成ルートにて調製した。市販の 3-アミノ 5-メチル安息香酸 **14** から 3 工程にてアルデヒド体 **15** を合成し、さらに Knoevenagel 縮合に続く水素添加を施すことでマロネート体 **16** とした。その後、別途調製したプロパルギルユニットを導入し基質 **17** を得た。また、アニリン部位の保護基を変換した基質 **18a** も合成した。

Scheme 2-9. Substrate synthesis



得られた **17** と **18a** を用いて Pd 触媒下における反応条件の検討を開始した(Table 2-1)。まず、Boc 体 **17** を先のスピロ環合成とベンゾフラン合成それぞれの最適条件に曝したところ、加溶媒分解やエステル交換などの副反応が起こるのみで目的環化体は全く得られなかった(entry 1,2) 。しかし、Ts 体 **18a** を反応基質とした際に、予想とは異なるものの、2 位にメチル基の導入されたインドール誘導体 **19a** がわずかながら確認された(entry 4)。

Table 2-1. Initial trial

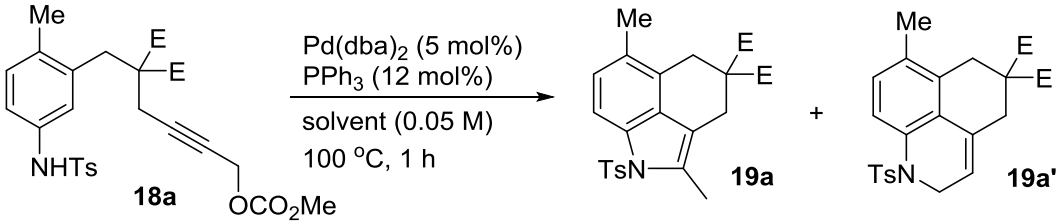


entry	R	solvent	temp (^{o}C)	time (h)	result [a] (%)
1	Boc	CH_2Cl_2/MeOH = 4/1	40	24	solvolysis
2	Boc	toluene/EtOH = 4/1	60	16	messy
3	Boc	THF/MeOH = 4/1	60	16	n.r
4	Ts	toluene/EtOH = 4/1	60	16	**23** (7%)
5	Ts	toluene/EtOH = 4/1	rt	24	solvolysis

[a] Isolated yield.

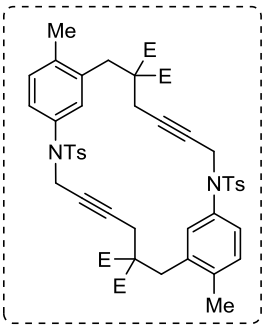
狙い通りの環化様式ではないものの、形式的には 3,4 位縮環型インドール類の生成が確認できたため、化合物 **19a** の収率向上を目指し更なる検討を行うこととした(Table 2-2.)。低収率の主な原因がアルコール溶媒であったことから、単一溶媒を用いて反応を行ったところ、わずかながら **19a** の収率が改善された。一方でジヒドロキノリン体 **19a'**と、分子間反応による複数の多量体が副生するという結果が得られた(entry 1)。さらに各種溶媒を検討したところ、非プロトン性の極性溶媒を用いた際に反応の選択性と収率の改善が見られた(entry 3,4)。以上の結果を受け、DMF を最適溶媒として選択した。

Table 2-2. Screening of solvent



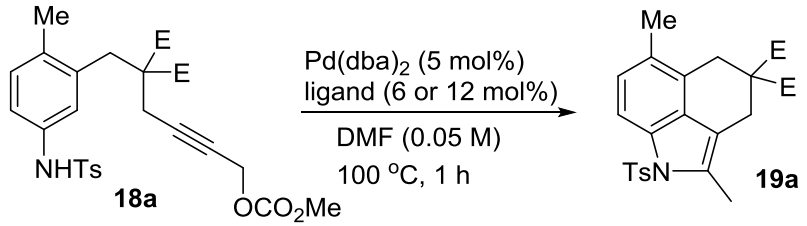
entry	solvent	yield of **19a**/**19a'**[a]
1	toluene	14% / 24%
2	dioxane	22% / 37%
3	DMF	37% / <5%
4	DMSO	31% / <5%

[a] Isolated yield.

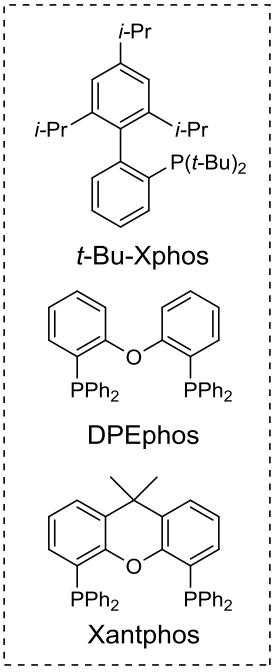


続いて配位子の検討を行った(Table 2-3.)。まず単座配位子について種々検討を行ったが、トリフェニルホスフィンよりも良い結果を与える配位子は見出せなかった(entry 1-6)。しかし、二座の Xantphos 配位子を用いた際に今までで最も良い収率にて目的物を与えた(entry 12)。また、求核性の低いプロトン性溶媒であるトリフルオロエタノールを系中に混在させて反応を行うこと、で若干収率が改善された(entry 13)。

Table 2-3. Screening of ligand



entry	ligand (mol%)	yield (%)[a]
1	PPh_3 (12)	37
2	$P(OPh)_3$ (12)	38
3	P(*p*-Cl)$_3$ (12)	trace
4	PCy_3 (12)	n.r
5	P(*t*-Bu)Ph_2 (12)	n.r
6	*t*-Bu-Xphos (12)	n.r
7	dppp (6)	28
8	dppb (6)	29
9	dppf (6)	30
10	(*R*)-BINAP (6)	33
11	DPEphos (6)	35
12	Xantphos (6)	64
13[b]	Xantphos (6)	75



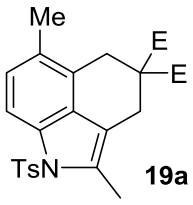
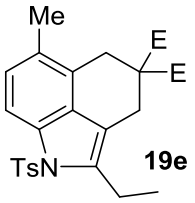
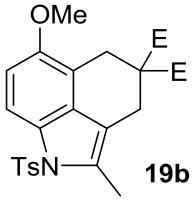
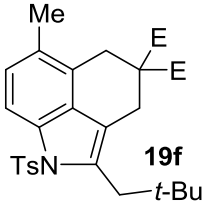
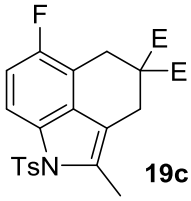
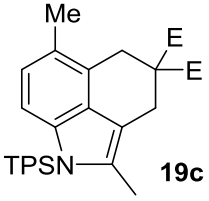
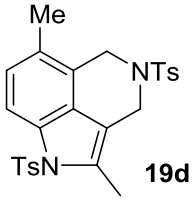
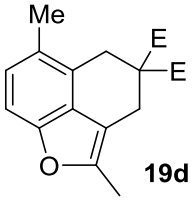
[a] Isolated yield.
[b] DMF/CF_3CH_2OH (4/1) was used as the solvent.

その他各種 Pd 触媒や塩基等についても検討を行ったが、収率の改善は見られなかった。

第四節　基質一般性の検討

得られた最適条件の下、基質一般性の検討を行った。パラ位の置換基を種々変換した基質や NTs で架橋した基質では多量体の生成が優先し、収率は低下した(entry 2–4)。三級のカーボネートを基質とした場合には多量体の生成こそ抑えられたものの、ジヒドロキノリン体や β 水素脱離の進行したエンイン体が副生した。なお、これらの基質において最も良好な結果を与えたのは dppb 配位子であった。(entry 5,6)。分子間反応の抑制を期待し嵩高い保護基を持つ基質でも検討を行ったが、結果は変わらなかった(entry 7)。求核部位をフェノールとした基質ではベンゾフラン誘導体が得られた(entry 8)。結果として、基質により収率に大きくバラつきが出た。原因として多量体やジヒドロキノリン体の副生が挙げられる。

Table 2-4. Scope and limitations

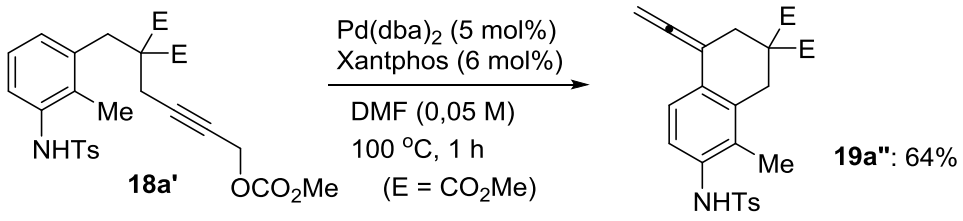
entry	product	results[a]	entry	product	results[a]
1	 **19a**	$Pd(dba)_2$, Xantphos DMF/TFE = 4/1 75% yield.	5	 **19e**	$Pd(dba)_2$, dppb DMF 40% yield.
2	 **19b**	$Pd(dba)_2$, Xantphos DMF 28% yield.	6	 **19f**	$Pd(dba)_2$, dppb DMF 27% yield.
3	 **19c**	$Pd(dba)_2$, Xantphos DMF 24% yield.	7	 **19c**	$Pd(dba)_2$, Xantphos DMF/TFE = 4/1 75% yield.
4	 **19d**	$Pd(dba)_2$, Xantphos DMF 29% yield.	8	 **19d**	$Pd(dba)_2$, Xantphos DMF 32% yield.

[a] Reaction proceeded at 100 °C for 1 h. Isolated yield.

第五節　反応機構の考察

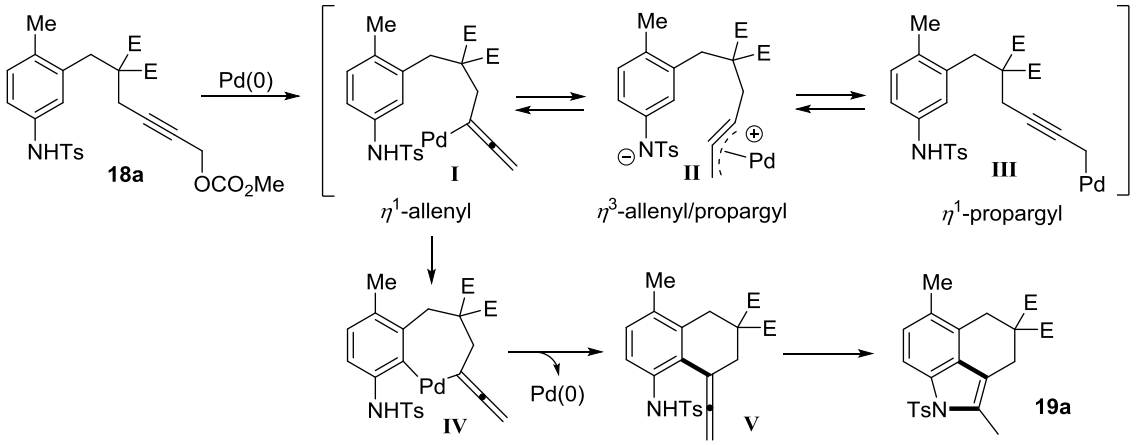
インドール誘導体 **19a** を与える連続環化の反応機構を解明すべく、検討を行った。まず中間体の単離を試みたが、**18a** を基質とした場合の環化速度は非常に早かったため反応時間や温度の調節では得られなかった。一方、以下に示す芳香環オルト位の反応点を潰した基質 **18a'**を用いて反応を行ったところ、パラ位で反応の進行したアレン体 **19a"**が得られた。

Scheme 2-10. Pd-catalyzed cyclization of **18a'**



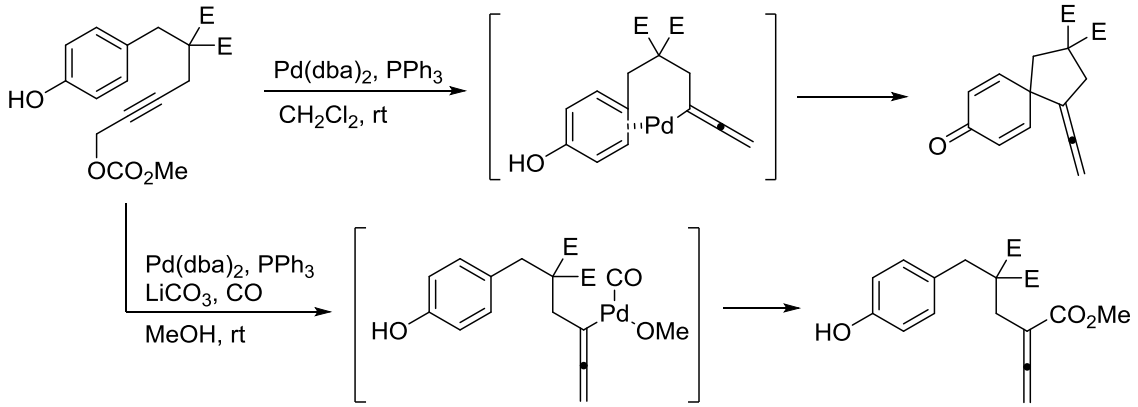
すなわち、本反応はアレン型中間体を経由していると予想される。以上の結果から推測される反応機構について下図に示す。まず基質の酸化的付加により、カーボネートの脱離を伴いアレニル/プロパルギル錯体平衡混合物(**I-III**)が形成される。本来であれば錯体 **II** に対する分子内 Friedel–Crafts 型の付加反応を期待したが、実際はおそらく錯体 **I** を経由して反応が進行したものと思われる。すなわち、錯体 **I** の Pd 原子上に芳香環が配位し、生じた７員環パラダサイクル **IV** が還元的脱離を受けることでアレン型中間体 **V** へと導かれたものと予想できる。最後に中間体 **V** のアニリン窒素がアレン中心炭素へ求核付加を起こすことで **19a** を与える。

Scheme 2-11. Proposed reaction mechanism of the formation of **19a**



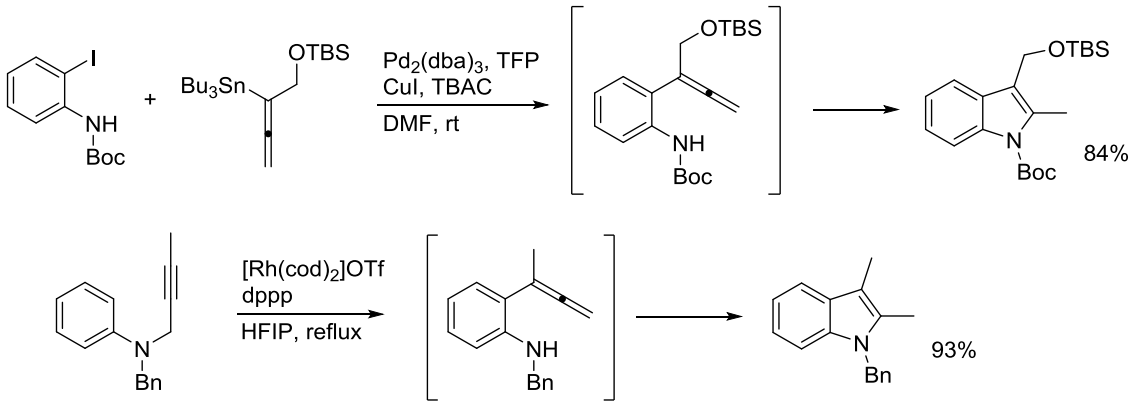
このη[1]-アレニル錯体（錯体 **I**）に関しては、先行研究であるスピロ環合成においても観測されており、実際速度論下における主生成物は本錯体由来のアレン体であることが確認されている。また、一酸化炭素雰囲気化において反応を行った場合には、一部η[1]-アレニル錯体由来の挿入反応が進行することもわかっており、本錯体が反応活性種になり得ることが十分に予想される[24]。

Scheme 2-12. Spirocyclization and CO insertion via η^1-allenyl palladium complexes



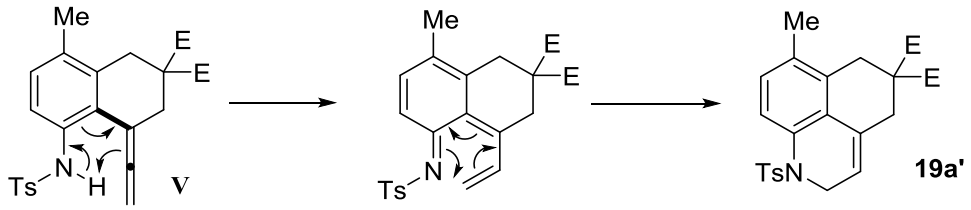
また、二つ目の環化段階であるアレン中心炭素への求核攻撃に関しては、いくつか反応が知られている。実際に同様の手法にて 2 位置換型インドール誘導体を合成している例を以下に示す[35]。

Scheme 2-13. Synthesis of 2-substituted indoles from allene derivatives



また、ジヒドロキノリン体 **19a'**についてはアレン型中間体 **V** のプロトン移動に続く 6π電子環状反応により生成したものと考察している[36]。

Scheme 2-14. Possible reaction mechanism of the formation of **19a'**

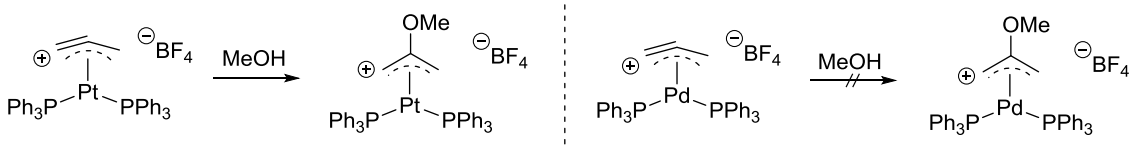


第六節　η^3-アレニル/プロパルギル錯体に関する考察

形式的な 3,4 位縮環型インドール誘導体の合成には成功したものの、得られた **19a** はインドール 2 位にメチル基を有しているため実用性に欠け、その反応自体も収率や基質一般性に乏しいものであった。そこで当初の計画通り、η^3-アレニル/プロパルギル錯体由来の環化体を得るべく更なる検討を行うこととした。

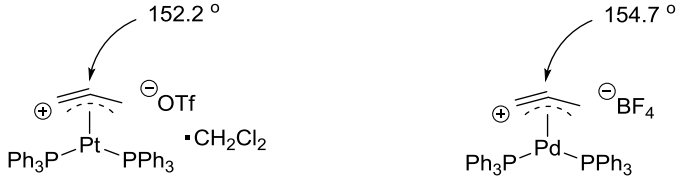
η^3-アレニル/プロパルギル錯体の性質については、９０年代中頃から００年代前半にかけて生越、黒沢らによって精力的に研究されている [37]。特に彼らはパラジウム錯体と白金錯体に関して綿密な検討を行っており、その報告の中でη^3-アレニル/プロパルギル白金錯体はパラジウム錯体に比べて求核剤との反応性が高いと述べている。実際に単離したそれぞれの錯体に MeOH を添加した場合、白金錯体でのみ反応が進行することを確認している [37a]。

Scheme 2-15. The reactivity of η^3-allenyl/propargyl platinum/palladium complexes



なお、これら錯体に関しては Wojcicki らによって単結晶の X 線結晶構造解析が行われている [38]。それぞれの解析結果を比較すると、η^3-アレニル/プロパルギル錯体の中心炭素は、白金錯体の方がパラジウム錯体よりも鋭角になっていることがわかる。おそらく、この屈折角が反応性の違いを引き起こしているものと推測される。

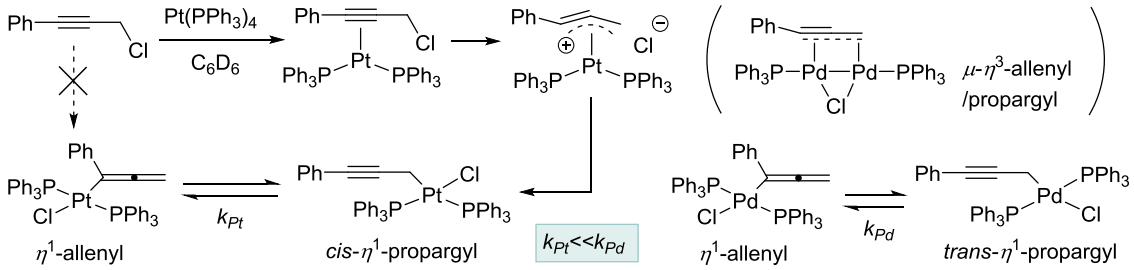
Figure 2-2. The structure of allenyl/propalgyl metal complexes



反応性の違いはそれぞれの原子の性質からも説明できる。Pt 原子は Pd 原子に比べて電気陰性度が高いため、配位子の電子密度が下がり求核剤との反応性が上がると考えられる。また、Pd 原子の基底電子配置は d^{10} であるのに対し、Pt 原子の基底電子配置は d^9s^1 であることが知られている。つまり、Pd 原子は 0 価の状態を好むのに対し、Pt 原子は 2 価の状態を好む。そのため、η^3-アレニル/プロパルギル錯体への付加成績体であるメタラシクロブテン環は、パラダサイクルよりもプラタナサイクルの方が安定に存在できる。おそらく、この生成物の熱力学的な安定性も、反応性の差異に影響を与えていると思われる。

また、プロパルギルクロリドの Pt(0)への酸化的付加によって得られる速度論生成物は、η^1-アレニル錯体ではなくη^3-アレニル/プロパルギル錯体であると述べられている [37c]。さらに、η^1-アレニル/プロパルギル錯体の異性化速度は、μ-η^3-allenyl/propargyl 錯体の存在によりパラジウム錯体の方が圧倒的に早いことも明らかにしている。つまり、白金錯体はパラジウム錯体に比べη^1-アレニル錯体を形成しにくいと予想できる [37d]。

Scheme 2-16. The reactivity of η^3-allenyl/propargyl platinum/palladium complexes

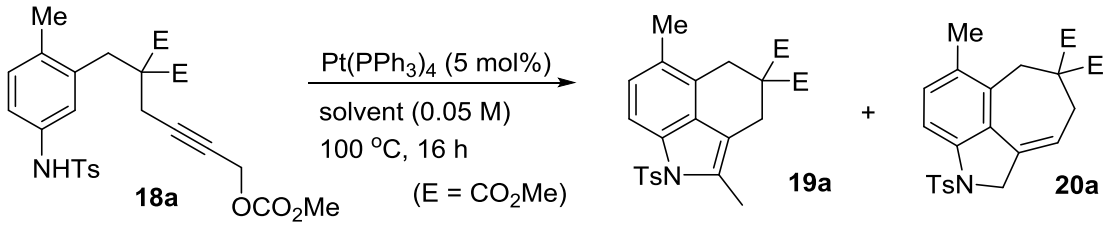


以上の知見より、η^3-アレニル/プロパルギルを介した反応系を構築するのであれば、パラジウム触媒ではなく白金触媒を用いるのが適当であると判断した。そこで 0 価白金触媒を軸とした **18a** の環化反応の再検討に着手した。

第七節　Pt 触媒を用いた検討

容易に入手可能な 0 価白金触媒として $Pt(PPh_3)_4$ を選択し、各種溶媒のスクリーニングを行った(Table 2-5.)。toluene や dioxane などの非極性溶媒を用いた場合にはこれまで同様 **19a** が生成するのみであったが、DMF 溶媒中で反応を行った際に低収率ではあるが目的環化体 **20a** が得られた(entry 3)。更なる検討の結果、DMSO 溶媒を用いると 88%収率にて環化体 **20a** を与えることを見出した(entry 4)。

Table 2-5. Pt(0)-catalyzed intramolecular Friedel–Crafts type cyclization

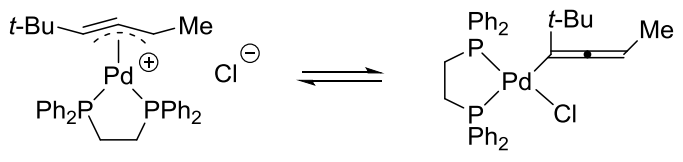


entry	solvent	yield of **19a** (%)	yield of **20a** (%)
1	toluene	<5	-
2	dioxane	30	-
3	DMF	13	31
4	DMSO	5	90 (88)[a]

Yields were determined by crude ^{1}H-NMR.
[a] Isolated yield.

この顕著な溶媒効果については、反応系中における錯体平衡の偏りに起因するものと考察している。生越、黒沢らは実際に各重溶媒中におけるアレニル/プロパルギル錯体の存在比を NMR にて測定しており、極性溶媒中においてはη^3錯体の形成が有利であることを明らかにしている [37f]。おそらく、誘電率の高い極性溶媒がカチオン性錯体を安定化させるためと思われる。また、配位性溶媒により求核部位のアニオンがむき出しにされ、求核性が向上したという見方もできる。

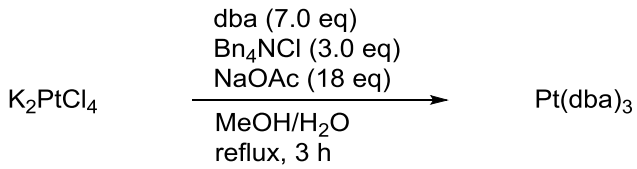
Scheme 2-17. Solvent effect on the ratio of allenyl/propargyl complexes



solvent	η^3/η^1
$CDCl_3$	75/25
DMF-d_7	99/1
C_6D_6	0/100

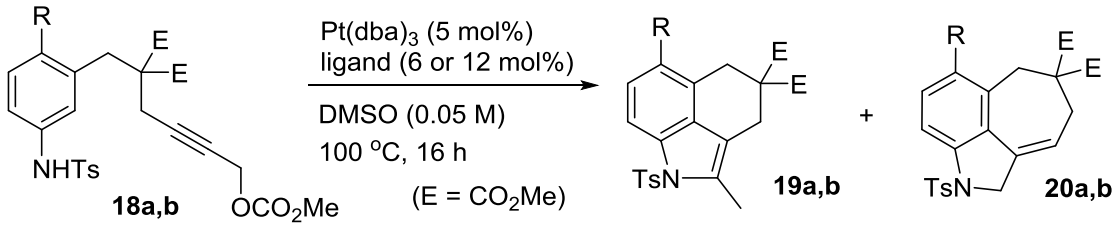
続いて配位子の検討を行った。その際、より配位子交換の容易な $Pt(dba)_3$ を Morken らの手法に基づいて調製し、触媒として使用した [39]。

Scheme 2-18. Preparation of $Pt(dba)_3$



$Pt(dba)_3$ 存在下配位子のスクリーニングを行った結果、二座配位子 dppp 用いた場合には反応性が低下し、dppf や Xantphos を用いると反応は複雑化した。一方で DPEphos を用いた際には PPh_3 と同程度の反応性を示した上、PPh_3 では中程度の収率であった化合物 **20b** も収率良く与えた。以上の結果より、DPEphos を最適配位子として用いることとした。配位子の効果に関しては考察が難しいが、パラジウムの場合は一般的に二座配位子の方が η^3錯体を安定化できるとされる。今回、比較的配位挟角の広い配位子を用いることで、原子半径の大きい白金触媒でも η^3錯体を上手く安定化させられたのではないかと考えている [37f]。

Table 2-6. Screening of ligand



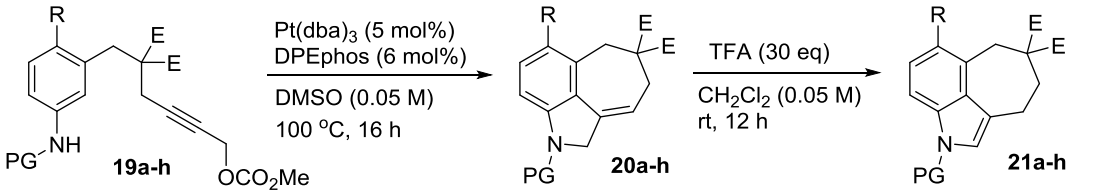
entry	substraate	R	ligand (mol%)	yield of **19** (%)	yield of **20** (%)
1	**18a**	Me	PPh_3 (12)	<5	89
2	**18a**	Me	dppp (6)	<5	7
3	**18a**	Me	dppf (6)	<5	45
4	**18a**	Me	DPEphos (6)	<5	90
5	**18a**	Me	Xantphos (6)	<5	21
6	**18b**	F	PPh_3 (12)	<5	47
7	**18b**	F	DPEphos (6)	<5	91

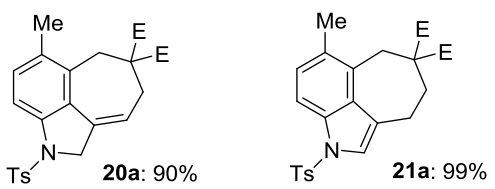
Yields were determined by crude ^{1}H-NMR.

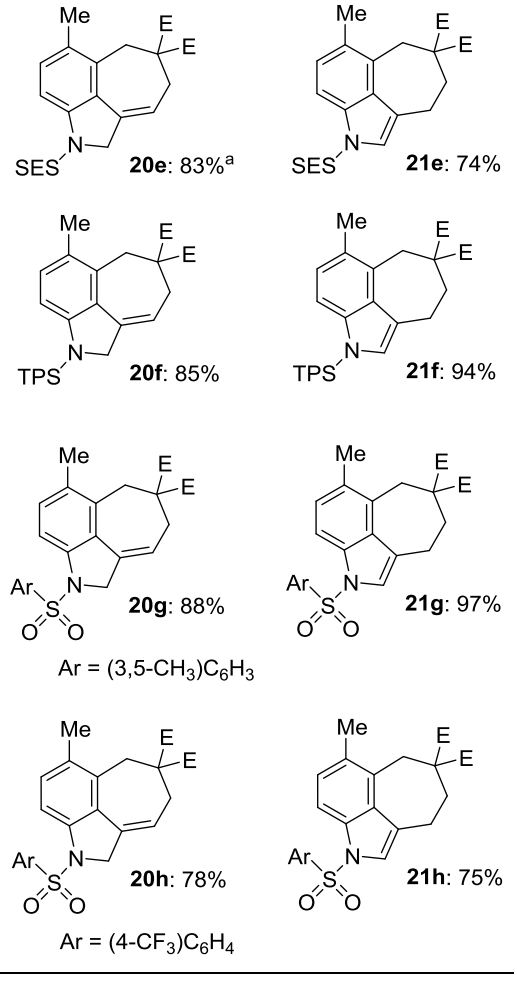
第八節　基質一般性の検討

最適条件の下、基質一般性の検討を行った(Table 2-7.)。パラ位置換基が電子供与性基や求引性基であっても問題なく反応は進行し、保護基は Ms 基や SES 基、芳香環上に種々置換基の導入されたスルホニル基への変換も可能であった。

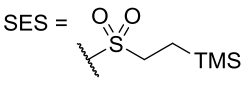
Table 2-7 (1). Scope and limitations

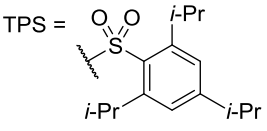






[a] 10 mol% of $Pt(dba)_3$, 12 mol% of DPEphos.

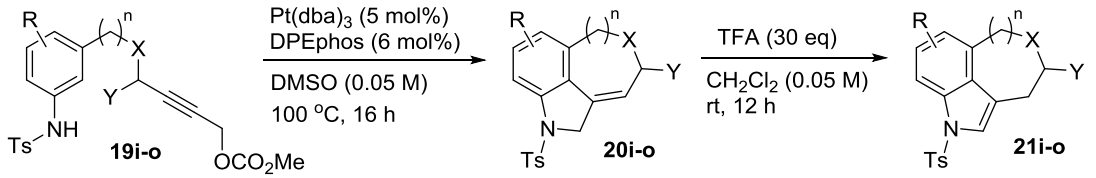


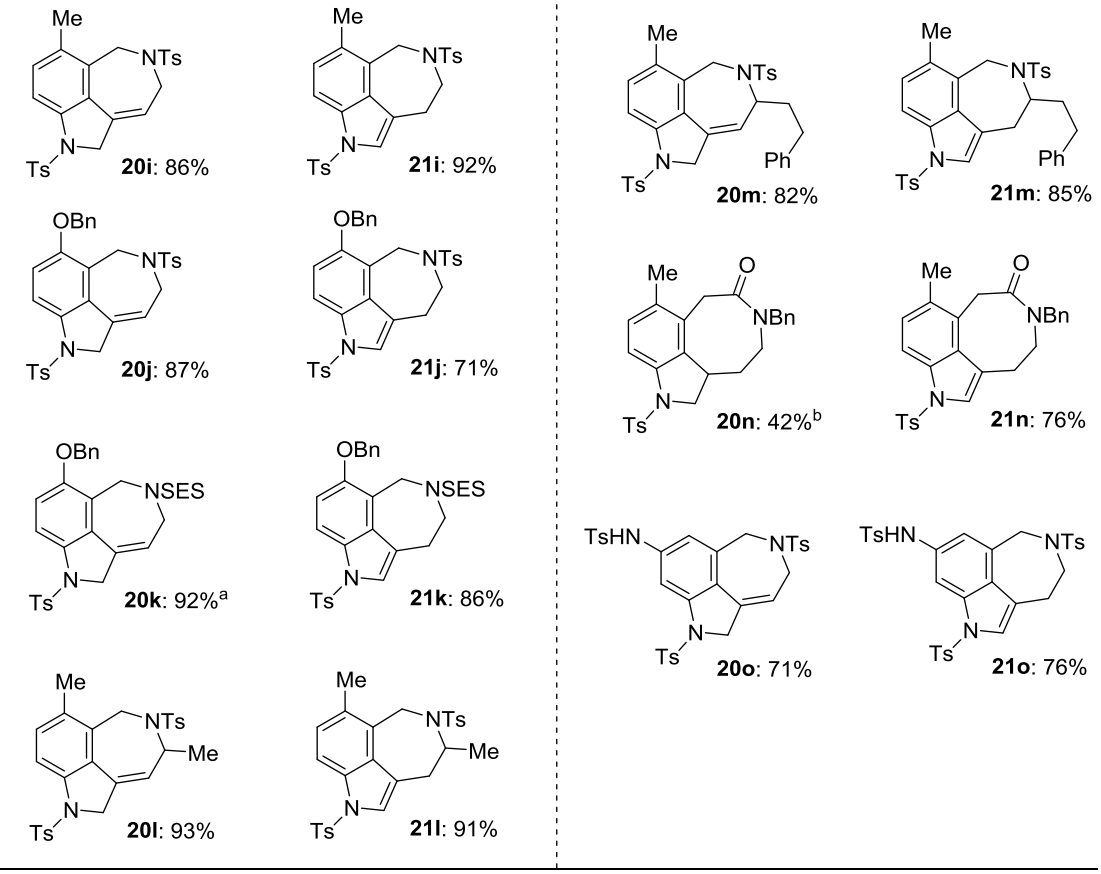


側鎖の架橋部位を窒素官能基とした基質でも効率良く反応は進行し、プロパルギル位に置換基を導入しても問題は無かった。また、一炭素増炭されたアミドで架橋された基質においても、触媒量を必要とはするものの八員環の構築が可能であった。求核部位が対称のアニリン誘導体であれば、パラ位置換基が無くても反応は効率良く進行した。

なお、これら環化体はいずれもトリフルオロ酢酸で処理することで容易にインドール体へと導くことが可能である。

Table 2-7 (2). Scope and limitations

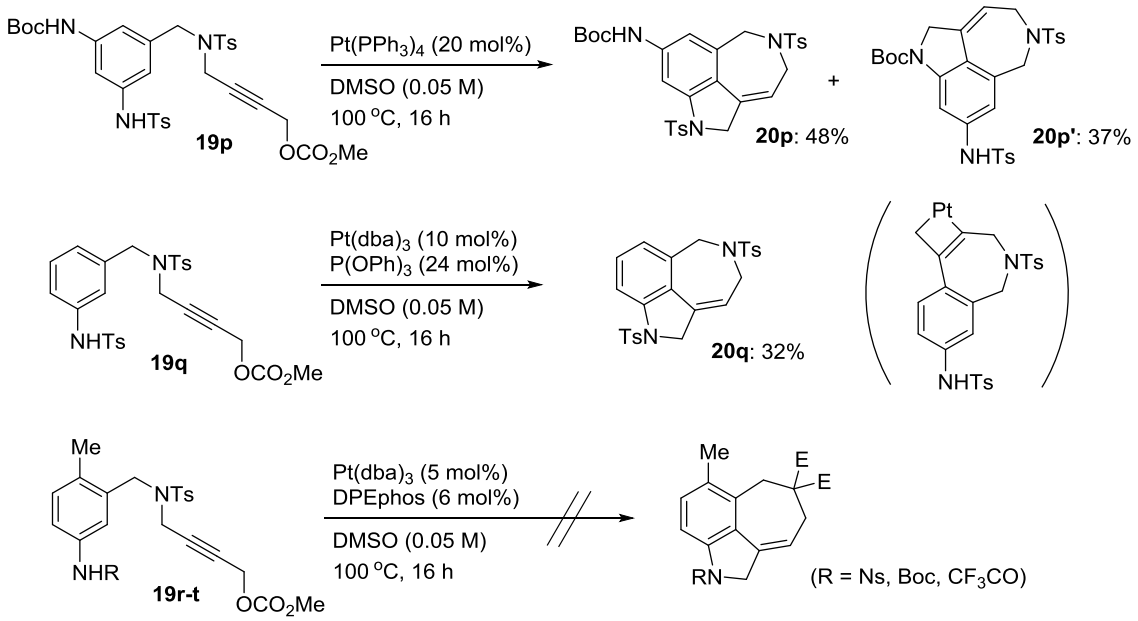




[a] 10 mol% of $Pt(dba)_3$, 12 mol% of DPEphos. [b] 20 mol% of $Pt(dba)_3$, 24 mol% of DPEphos.

また、求核部位を非対称とした基質の場合には、トシルアニリドのパラ位でも環化が進行した化合物 **20p'**が得られた。一方、置換基の存在しない基質では収率が低下し、原料の残存と一部二量体の副生が確認された。二量体の構造は明らかでないが、おそらくアニリンのパラ位に環化が進行した後に分子間反応が進行したものと考えている。なお、アニリンの保護基を Ns 基や Boc 基、トリフルオロアセチル基とした場合には、反応は全く進行しなかった。Ns 基の場合は芳香環の電子密度が低下し、Friedel–Crafts 型反応が進行しにくくなったと考えられる。また、ニトロ基が酸化剤として機能し、白金触媒を失活させたという可能性も否定できない。Boc 基や TFA 基に関しては、アニリド水素の酸性度が十分ではないために、脱離基であるカーボネートによって脱プロトン化されなかったのではないかと考えている。

Scheme 2-19. Scope and limitations



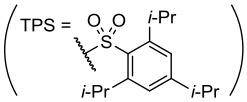
η^3-アレニル/プロパルギル錯体を活性種とした触媒反応は、調べ得る限りパラジウム触媒による報告しか存在せず、白金触媒を実践的有機合成へと応用したのは本例が世界初である。一般的に２価白金錯体は対応するパラジウムやニッケル錯体に比べ、はるかに安定に存在することが知られている。そのため、白金錯体は従来錯体合成や当量反応の用途で使用されてきた。今回、反応の触媒化に成功した要因として、スルホンアミドの存在が何かしらの影響を与えていると予想している。現時点で詳細は解明できていないが、今後様々な基質を用いた検討によりそのメカニズムを明らかにし、０価白金触媒反応の応用例を増やしていきたいと考えている。

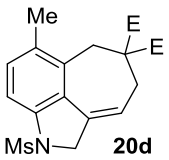
第九節　生物活性評価

合成した化合物群に関して、白血病細胞 HL60、胃癌上皮細胞 AGS、大腸癌細胞 RKO に対する活性評価を行った。インドリン体 **20d** は AGS に対する活性が見られるのみであったが、**20f** は HL60 及び AGS に対する強い増殖抑制作用を有することが明らかとなった。また、インドール体に関しても **21d** に比べて **21f** の方が HL60 並びに AGS 細胞に対する活性が高いことが明らかとなった。以上の結果より、スルホンアミド上の置換基が何らかの活性発現に関与している可能性が示された。また、**21d** に関しては RKO に対する活性も確認された。

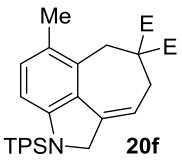
さらに、これら化合物群に関して正常細胞 WI38 及び IMR90 に対する毒性評価も行ったところ、いずれも毒性を示さないことが明らかとなった。本結果は 3,4 位縮環型インドリン及びインドール誘導体が抗癌剤シードに成り得る可能性を示すと共に、開発した反応が創薬研究において有用であることを立証するものである。

Table 2-8. Antiproliferative activities of reaction products

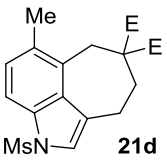




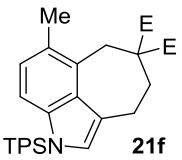
20d



20f



21d



21f

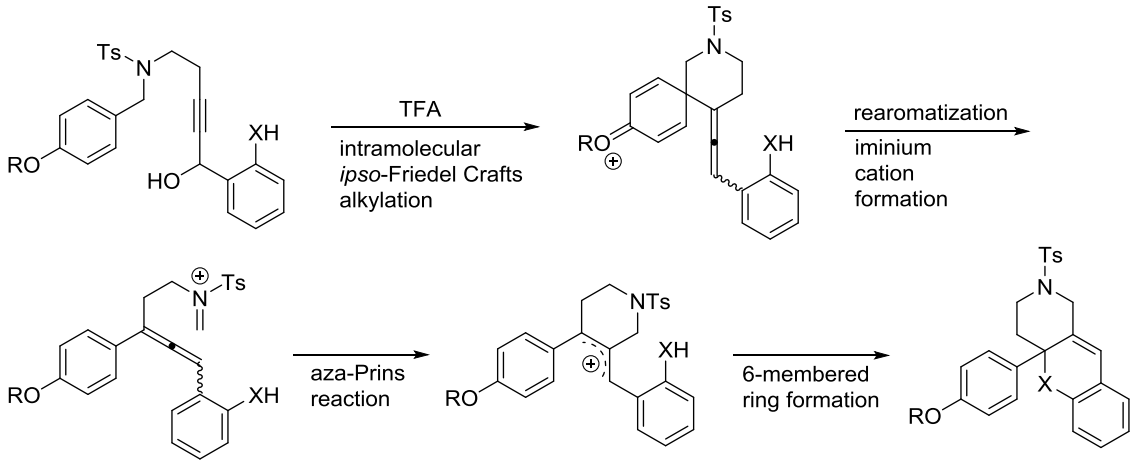
Cell line	**IC^{50} Value (μM)**			
HL60 (Leukemia)	>10	1.02	4.98	1.41
AGS (Stomach)	7.92	1.45	>10	1.77
RKO (colon)	>10	>10	8.47	>10
WI38 (normal)	>10	>10	>10	>10
IMR90 (normal)	>10	>10	>10	>10

第三章　酸により促進されるカスケード環化反応を利用した 4,5 位縮環型キノリン誘導体効率合成法の開発

第一節　背景

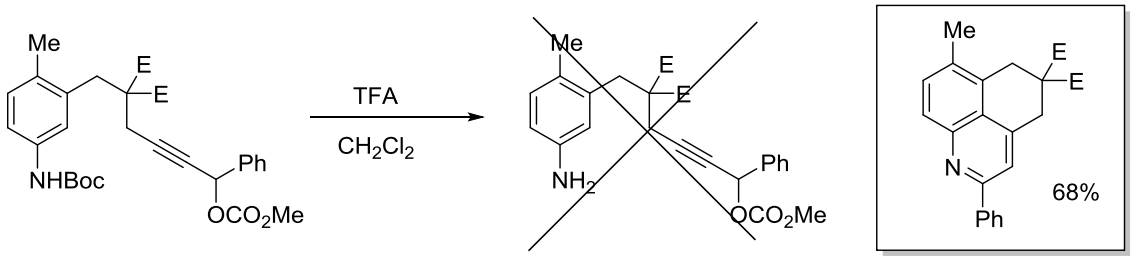
酸による連続環化は自然界においても良く見られる反応であり、時に反応予測が困難なほど複雑な縮環体を与えうる[40]。当研究室の横坂は最近、下図に示すプロパルギルアルコール部位を有するアニソール誘導体を酸で処理すると、Friedel–Crafts 反応を基盤とした特徴的なカスケード反応が進行することを見出した[41]。本基質はプロパルギル位がアリール側鎖により活性化されており、そこに酸による S_N2'型の分子内 *ipso*-Friedel–Crafts アルキル化が進行することで反応が開始する。

Scheme 3-1. Construction of divergent fused heterocycles via an acid-promoted cascade cyclization



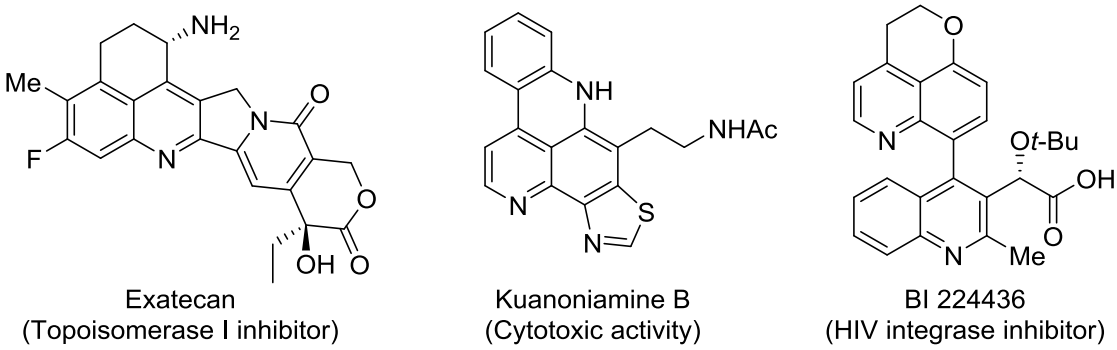
一方、3,4 位縮環型インドール合成研究における基質合成の際、同じようにフェニル基で活性化されたプロパルギルユニットを有するメタ置換型のアニリン誘導体を TFA で処理したところ、下図に示す縮環キノリン体を収率良く与えた。おそらく、本反応も分子内 Friedel–Crafts アルキル化を足掛かりに連続環化が進行したものと思われる。

Scheme 3-2. Acid-promoted cascade cyclization of an aniline derivative



キノリン環は数多くの生物活性天然物や市販医薬品に含まれる構造であり、しばしば活性発現に重要な役割を担っている[42]。この医薬化学的に興味深い構造から、キノリン環の効率的合成法に関しては現在でも活発に開発研究が行われている。今回得られた 4,5 位縮環型キノリン骨格は、生物活性天然物 Kuanoniamine B[43] や抗癌剤 Exatecan[44]、医薬品候補化合物 BI 224436[45] に共通して含まれる構造であり、医薬品シードに成り得る可能性を秘めている。

Figure 3-1. Examples of bioactive compounds which contain 4,5-fused quinolines

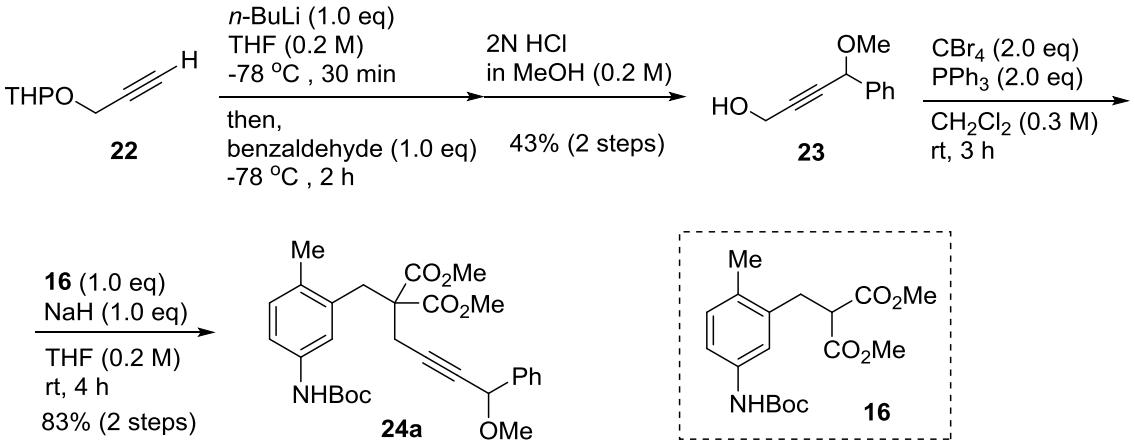


すなわち、本反応に関しても条件を一般化することで創薬研究への寄与が期待される。以上の背景の下、酸による 4,5 位縮環キノリン誘導体の効率合成法の開発を目指し、検討を開始した。

第二節　反応条件の最適化

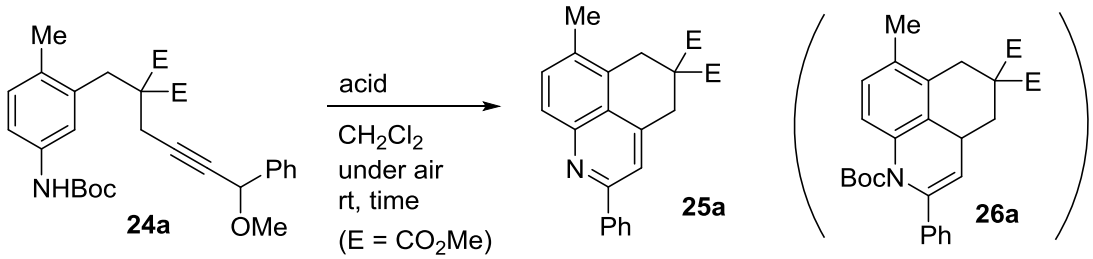
脱離基をより単純化した化合物 **24a** を用いて反応条件の検討を行うこととし、基質を以下のように合成した。市販されているアルキン **22** の末端をリチオ化しベンズアルデヒドへ付加させた後、塩酸/メタノール中で撹拌することで THP 基の脱保護とメトキシ基への変換を同時に行った。続いて得られた **23** の水酸基を Appel 反応にて臭素化し、マロネート **16** を導入することでモデル基質 **24a** とした。

Scheme 3-3. Substrate synthesis



合成した **24a** を用い、条件の最適化を行った(Table 3-1)。まず CH_2Cl_2 中 TFA を 3 当量用いて反応を行ったところ、環化こそスムーズに進行したものの、Boc 基が残った化合物 **26a** を主生成物として与えた(entry 1)。そこで TFA の当量を徐々に増やしていったところ、15 当量用いた際に Boc 体 **26a** を完全にキノリン体 **25a** へと変換させることに成功した(entry 2)。続いて、副生していると思われる多量体を抑制すべく、溶媒濃度に関して検討を行った。しかし、0.05 M よりも濃くすると収率は低下し(entry 5)、薄くしても収率は改善されず反応時間が延長されるのみであった(entry 6)。また、TsOH を酸として用いると反応は複雑化した(entry 7)。おそらく、カウンターアニオンがカチオンに緩く配位することが反応の促進に影響していると思われる。以上の結果より、0.05 M CH_2Cl_2 中 TFA を 15 当量用いる条件を採用することとした。

Table 3-1. Optimization of the reaction conditions



entry	acid (eq)	concd (M)	time (h)	yield (%)[a]
1	TFA (3)	0.05	16	12 (50)[b]
2	TFA (8)	0.05	16	60
3	TFA (15)	0.05	3	76
4	TFA (25)	0.05	3	75
5	TFA (15)	0.1	3	67
6	TFA (15)	0.025	12	74
7	TsOH·H_2O (3)	0.05	3	messy

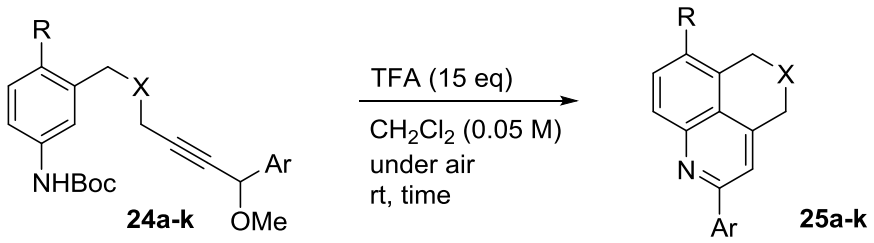
[a] Determined be ^{1}H-NMR analysis of the crude sample.

[b] Isolated yield of byproduct.

第三節　基質一般性の検討

得られた最適条件の下、基質一般性の検討を行った(Table 3-2)。側鎖のアリールはオルト位、メタ位、パラ位いずれの位置に置換基が導入されても反応は進行した(entry 2–8)。しかし、パラ位がハロゲンで置換された基質に関しては多量体の副生が増加したため、溶媒濃度を薄めて反応を行う必要があった(entry 4,5)。また、求核部位であるアニリンのパラ位が種々変換された基質に関して、電子供与性基の場合は問題なく反応が進行したものの、求引性基の場合若干反応性の低下が確認された(entry 9,10)。また、側鎖が NTs で架橋された基質では大きく反応性は低下した(entry 11)。これはおそらく、sp2 炭素が導入されることで側鎖の柔軟性が失われたためと思われる。

Table 3-2. Scope and limitations



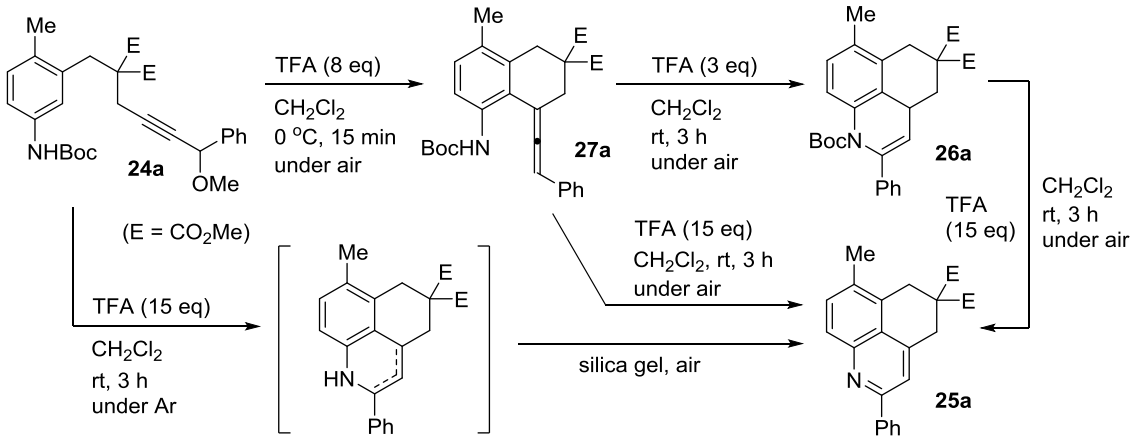
entry	product	R	X	Ar	yield (%)[a]
1	**25a**	Me	$C(CO_2Me)_2$	C_6H_5	75
2	**25b**	Me	$C(CO_2Me)_2$	4-MeC_6H_4	53
3	**25c**	Me	$C(CO_2Me)_2$	4-$OMeC_6H_4$	62
4[b]	**25d**	Me	$C(CO_2Me)_2$	4-ClC_6H_4	60
5[b]	**25e**	Me	$C(CO_2Me)_2$	4-BrC_6H_4	69
6	**25f**	Me	$C(CO_2Me)_2$	3-$OMeC_6H_4$	84
7	**25g**	Me	$C(CO_2Me)_2$	3-MeC_6H_4	79
8	**25h**	Me	$C(CO_2Me)_2$	2-MeC_6H_4	82
9	**25i**	OMe	$C(CO_2Me)_2$	C_6H_5	75
10	**25j**	F	$C(CO_2Me)_2$	C_6H_5	53
11[b]	**25k**	Me	NTs	C_6H_5	31

[a] Isolated yield.
[b] Reaction concentration = 0.025 M.

第四節　反応機構の解析

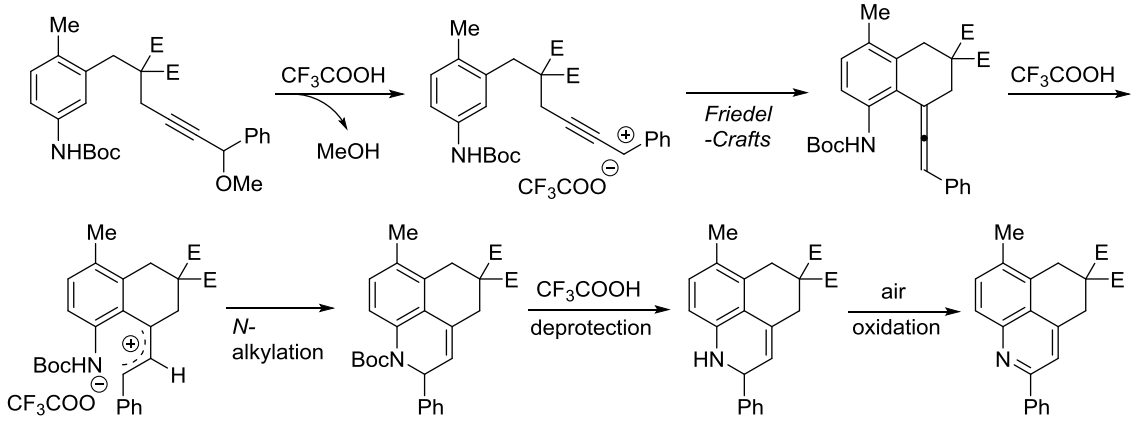
詳細な反応機構を解明すべく、中間体の同定を試みた。低温下、反応を 15 分で止めたところ、予想中間体であるアレン体 **27a** を単離した。さらに **27a** を 3 当量の TFA にて処理すると、更なる環化反応が進行し Boc 体 **26a** を与えた。また **26a**、**27a** 共に過剰量の TFA に曝すと、キノリン体 **25a** へと導かれることも確認した。なお、単離することはできなかったものの、アルゴン化にて反応を行った際にはジヒドロキノリン体の生成を観測した。

Scheme 3-3. Experiments for elucidating the reaction pathway



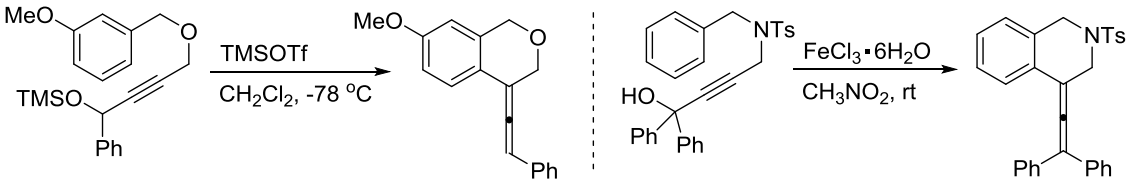
以上の実験結果より、反応機構を以下のように推測した。まずメトキシ基がプロトン化を受け脱離し、生じたプロパルギルカチオンに対して分子内Friedel–Crafts反応が進行することでアレン体**27a**を与える。その後、アレン部位が再度プロトン化を受けることでアリルカチオンが生じ、窒素原子からの分子内環化が進行することでBoc体を**27a**与える。最後に脱保護、酸化が連続的に進行し、キノリン体**25a**が生成したものと思われる。

Scheme 3-4. Proposed reaction mechanism



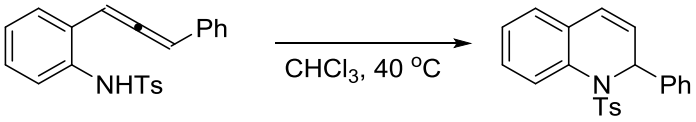
本反応機構を支持する結果として、Lewis 酸を用いた分子内 Friedel–Crafts 反応による同種の縮環アレン合成反応が、斎藤らと Zhou らによってそれぞれ独立に報告されている [46]。

Scheme 3-5. Intramolecular Friedel–Crafts allenylation



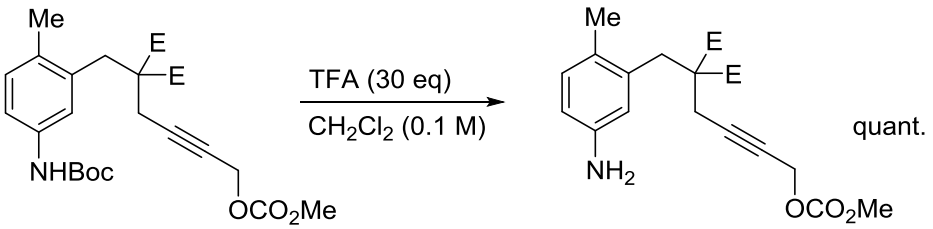
二段階目の環化に関しても、最近 Bi らによって同種の反応が報告されている [47]。フェニル基置換されたアレン型基質をクロロホルム中熱処理することで、位置選択的な 6-*endo* 環化が進行し、ジヒドロキノリン体を与える。

Scheme 3-6. Selective 6-*endo* cyclization of allenes



今回開発した反応は、過去の報告例と同様プロパルギル位がアリール基によって置換された基質においてのみ有効であった。つまり、カチオンが発生しやすい環境作りが必要不可欠であり、それを考慮した基質デザインが必須となる。実際、単純なプロパルギルカーボネート類を TFA で処理した場合には、脱 Boc 体のみが定量的に得られてきた。

Scheme 3-7. Control experiment.

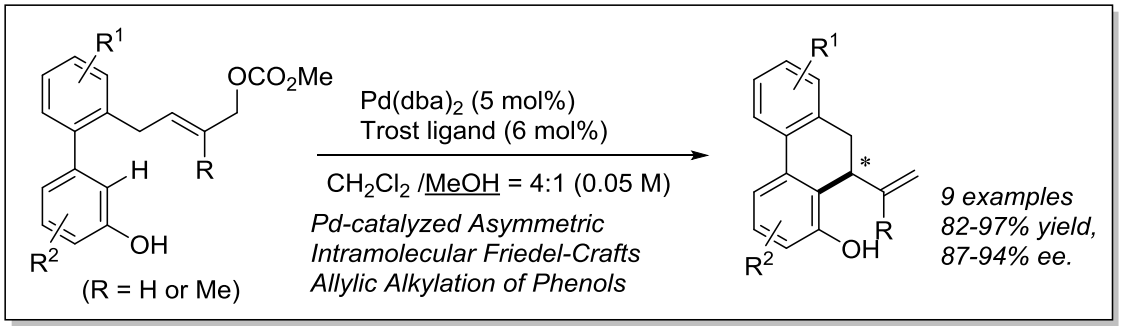


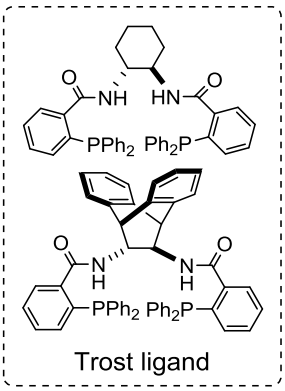
結語

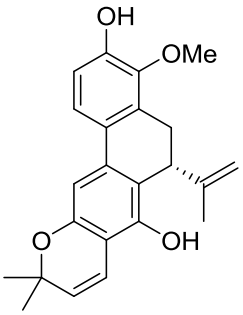
以上、筆者は分子内 Friedel–Crafts 型反応を基盤とした新規反応の開発研究に従事し、生物活性天然物や医薬品等に含まれる複雑縮環分子の新規効率合成法を開発した。各反応の要約を以下に記す。

① 9,10–ジヒドロフェナントレン類の触媒的不斉合成法開発と生物活性天然物合成[48–50]

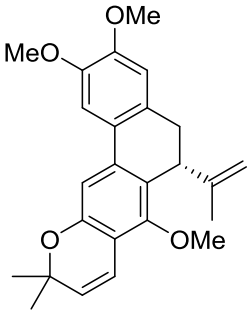
当研究室において開発された Pd 触媒による分子内 Friedel–Crafts 型アリル位アルキル化反応を応用し、メタ置換型フェニルフェノール誘導体を基質とした 9,10-ジヒドロフェナントレン類の新規不斉合成法へと昇華した。本反応ではメタノールとの混合溶媒条件下にて反応を行うことで競合する分子間反応が抑制され、目的環化体を高収率にて与えることを見出した。反応の不斉化にも成功しており、Trost 配位子を用いることで 10 位不斉点の制御されたジヒドロフェナントレン類を非常に効率良く与えることを見出した。さらに、本反応を用いた天然物 Cedrelin A 及び Paralycolin B の新規不斉全合成も達成した。







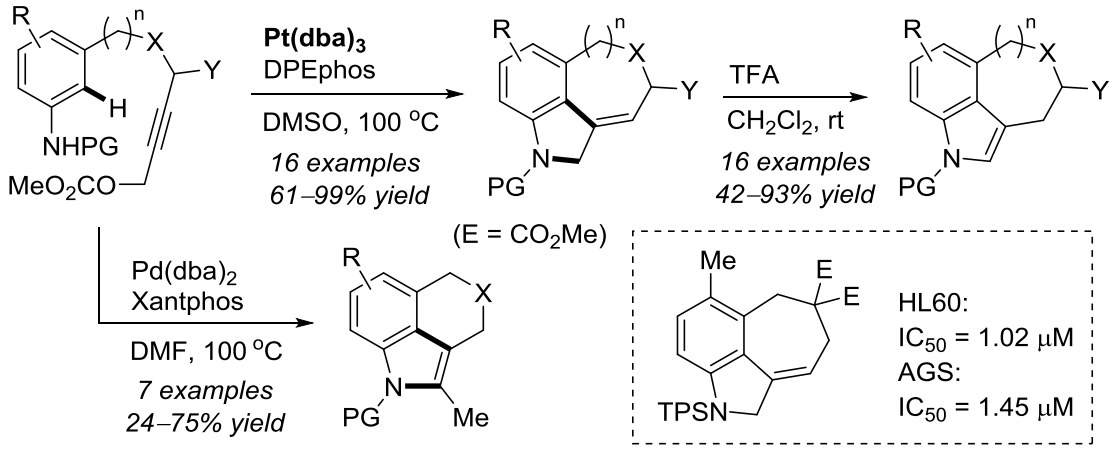
Cedrelin A
12 steps
16.5% yield,
66% ee.



methylated
Paralycolin B
10 steps
35.2% yield,
92% ee.

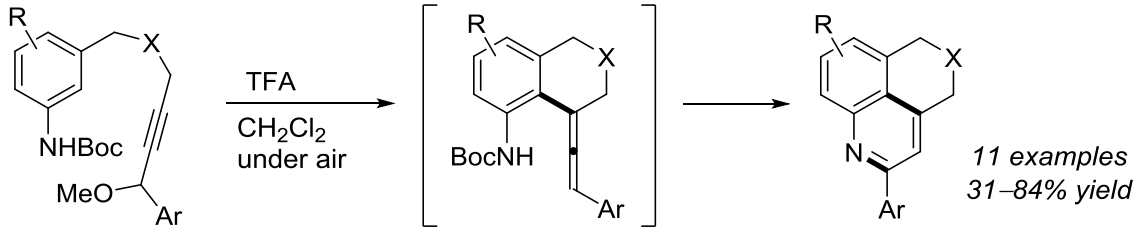
② 3,4 位縮環型三環性インドール骨格合成法の開発と生物活性評価[51,52]

アレニル/プロパルギル錯体の反応性を応用した分子内 Friedel–Crafts 型 C–H カップリング―アリル位アミノ化連続反応により、3,4 位縮環型三環性インドリン類及び、酸による転位を介したインドール類の新規効率合成法開発に成功した。本反応では、精密有機合成ではあまり利用されない 0 価白金触媒を用いた場合のみ、効率的に目的環化体を与えることを見出した。アレニル/プロパルギル白金錯体を活性種とした触媒反応は、調べ得る限り本例が世界初であり、アレニル/プロパルギルケミストリーの新たな可能性を切り拓いたと言える。また、パラジウム触媒を用いた場合には異なる縮環様式の 3,4 位縮環型インドール誘導体を与えることも見出し、その反応機構の解明も行った。さらに、合成した化合物群の活性評価を行うことで、その創薬シードとしての可能性も明らかにした。



③ 4,5 位縮環型三環性キノリン骨格合成法の開発[53]

アリール置換されたプロパルギルエーテル類に対し、過剰量のトリフルオロ酢酸を作用させることで分子内 Friedel–Crafts 反応と 6-*endo* 環化が連続的に進行することを見出し、4,5 位縮環型キノリン誘導体が効率的に得られることを見出した。また、反応条件を調節することで各中間体を単離し、詳細な反応機構を明らかにした。



References and Notes

1) For reviews, see: a) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921. b) Lu, Z.; Ma, Z. *Angew. Chem., Int. Ed*. **2008**, *47*, 258.

2) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. *J. Org. Chem*. **1999**, *64*, 2751.

3) Fern_andez, I.; Hermatschweiler, R.; Breher, F.; Pregosin, P. S.; Veiros, L. F.; Calhorda, M. J. *Angew. Chem., Int. Ed*. **2006**, *45*, 6386.

4) Trost, B. M.; Toste, F. D. *J. Am.Chem. Soc*. **1998**, *120*, 815.

5) a) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani–Ronchi, A. *J. Am. Chem. Soc*. **2006**, *128*, 1424. b) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett*. **2008**, *10*, 1815.

6) For other representative examples of transition metal-catalyzed asymmetric Friedel–Crafts allylic alkylation of heterocycles, see: a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc*. **2006**, *128*, 6314. b) Cheung, H. Y.; Yu, W.-Y.; Lam, F.-L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chen, A. S. C. *Org. Lett*. **2007**, *9*, 4295. c) Bandini,M.; Eichholzer, A. *Angew. Chem., Int. Ed*. **2009**, *48*, 9533. d) Wu., Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc*. **2010**, *132*, 11418. e) Hoshi, T.; Sasaki, K.; Sato, S.; Ishii, Y.; Suzuki, T.; Hagiwara, H. *Org. Lett*. **2011**, *13*, 932. f) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett*. **2011**, *13*, 2164. g) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci*. **2012**, *3*, 205. h) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed*. **2012**, *51*, 1680.

7) Nemoto, T.; Ishige, Y.; Yoshida, M.; Kohno, Y.; Kanematsu, M.; Hamada, Y. *Org. Lett*. **2010**, *12*, 5020.

8) Yoshida, M.; Nemoto, T.; Zhao, Z.; Ishige, Y.; Hamada, Y. *Tetrahedron: Asymmetry.* **2012**, *23*, 859.

9) a) Ezaki, K.; Satake, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett*. **1991**, *32*, 2793. b) Dell Monache, F.; Dell Monache, G.; Cavalcanti, J. F.; Pinheiro, R. M. *Tetrahedron Lett*. **1987**, *28*, 563. c) Dell Monache, F.; Dell Monache, G.; Botta, B.; Gacs-Baitz, E.; Recettori, C. C. *Heterocycles* **2002**, *56*, 589.

10) For recent selected examples of the synthesis of functionalized 9,10-dihydrophenanthrenes, see: a) Pratap, R.; Ram, V. J. *J. Org. Chem*. **2007**, *72*, 7402. b) Zhu, C.; Shi, Y.; Xu, M.-H.; Lin, G.-Q. *Org. Lett*. **2008**, *10*, 1243. c) Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K. *Org. Lett*. **2008**, *10*, 4795. d) Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. *Chem. Commun*. **2009**, 4284. e) Sustac Roman, D.; Takahashi, Y.; Charette, A. B. *Org. Lett*. **2011**, 13, 3242. f) Ueno, S.; Komiya, S.; Tanaka, T.; Kuwano, R. *Org. Lett*. **2012**, 14, 338.

11) For reviews, see: a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. b) Suzuki, A. *Angew. Chem., Int. Ed*. **2011**, *50*, 6722.

12) a) Hamada, Y.; Seto, N.; Ohmori, H.; Hatano, K. *Tetrahedron Lett*. **1996**, *37*, 7565. b) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett*. **1999**, *40*, 7791. c) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett*. **2001**, *42*, 1297. d) Hara, O.; Koshizawa, T.; Makino, K.; Kunimune, I.; Namiki, A.; Hamada, Y. *Tetrahedron* **2007**, *63*, 6170.

13) a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 9887. b) For a review on the MOP ligands, see: Hayashi, T. *Acc. Chem. Res*. **2000**, *33*, 354.

14) For a review on the chiral phosphoramidite ligands, see: Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed*. **2010**, *49*, 2486.

15) For a review on the PHOX ligands, see:Helmuchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, *33*, 336.

16) For recent selected examples of catalytic asymmetric reactions using the ANDEN-phenyl Trost ligand H, see: a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 3534. b) Trost, B. M.; Tang, W. *J. Am. Chem. Soc*. **2003**, *125*, 8744. c) Trost, B.M.; Frederiksen, M. U. *Angew. Chem., Int. Ed*. **2005**, *44*, 308. d) Trost, B.M.; Xu, J. *J. Am. Chem. Soc*. **2005**, *127*, 2846. e) Trost, B. M.; Xu, J. *J. Am. Chem. Soc*. **2005**, *127*, 17180. f) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc*. **2007**, *129*, 282. g) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc*. **2008**, *130*, 14092. h) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc*. **2009**, *131*, 12056. i) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. *J. Am. Chem. Soc*. **2010**, *132*, 8915. j) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc*. **2010**, *132*, 15534. k) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc*. **2011**, 133, 12439. l) Trost, B. M.; Sch€affner, B.; Osipov, M.; Wilton, D. A. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 3548.

17) See the Experimental Section for details.

18) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res*. **2006**, *39*, 747.

19) Lee, Y. R.; Choi, J. H.; Yoon, S. H.; *Tetrahedron Lett.* **2005,** *46*, 7539.

20) The ^{1}H and ^{13}C NMR data of methylated paralycolin B, reported by Delle Monache and co-workers in 2002 (Ref. 9c), were measured in C_6D_6, not in $CDCl_3$. Prof. Delle Monache kindly informed us this error information and provided us the NMR charts of methylated paralycolin B, measured in both C_6D_6 and $CDCl_3$. NMR data of our synthetic sample were identical to the provided data.

21) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H.; *J. Am. Chem. Soc*. **1998**, *120*, 1938.

22) For reviews of addition reactions to η^3-allenyl/propargyl platinum complexes, see: J.-T. Chen, *Coord. Chem. Rev*. **1999**, *190-192*, 1143. b) W.-C. Chiang, F.-Y. Tsai, Y.-C. Cheng, G.-H. Lee, Y. Wang, J.-T. Chen, *Inorg. Chim. Acta* **2002**, *334*, 213. c) R. T. Dunsizer, V. M. Marsico, V. Plantevin, A. Wojcicki, *Inorg. Chim. Acta* **2003**, *342*, 279.

23) For reviews, see: a) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley, hichester, 2004, Chapter 6. b) Ohno, H.; *Chem. Pharm. Bull*. **2005**, *53*, 1211. c) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M.; *Acc. Chem. Res*. **2011**, *44*, 111. d) Yoshida, M. *Chem. Pharm. Bull*. **2012**, *60*, 285.

24) Nemoto, T.; Zhao, Z.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed*. **2013**, *52*, 2217.

25) After published our paper, some related Pd-catalyzed Friedel–Crafts type addition reactions of indols were reported, see: a) Iwata, A.; Inuki, S.; Oishi, S.; Fuji. N.; Ohno, H. *Chem. Commun*. **2014**, 50, 298. b) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett*. **2014**, *16*, 3480. c) Gao, R.-D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett*. **2014**, *16*, 3919.

26) a) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett*. **2011**, *13*, 5636. b) Peshkov, V. A.; Van Hove, S.; Donets, P. A.; Pereshivko, O. P.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Eur. J. Org. Chem*. **2011**, 1837. c) Schö nherr, H.; Leighton, J. L. *Org. Lett*. **2012**, *14*, 2610. d) Hellal, M.; Singh, S.; Cuny, G. D. *J. Org. Chem*. **2012**, *77*, 4123. e) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci*. **2013**, *4*, 97.

27) For recent natural product syntheses based on this strategy, see the following. Aurantioclavine: a) Yamada, K.; Namerikawa, Y.; Haruyama, T.; Miwa, Y.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem*. **2009**, 5752. b) Brak, K.; Ellman, J. A. *Org. Lett*. **2010**, *12*, 2004. Clavicipitic acid: c) Xu, Z.; Li, Q.; Jia, Y. *J. Org. Chem*. **2009**, *74*, 6859. d) Bartoccini, F.; Casoli, M.; Mari, M.; Piersanti, G. *J. Org. Chem*. **2014**, *79*, 3255. Lysergic acid: e) Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett*. **2008**, *10*, 5239. f) Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem*.

2011, *76*, 5506. g) Liu, Q.; Jia, Y. *Org. Lett*. **2011**, *13*, 4810. h) Umezaki, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett*. **2013**, *15*, 4230. Serotobenine: i) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc*. **2008**, *130*, 16854. Decursivine: j) Leduc, A. B.; Kerr, M. A. *Eur. J. Org. Chem*. **2007**, 237. k) Sun, D.; Zhao, Q.; Li, C. *Org. Lett*. **2011**, *13*, 5302. l) Qin, H.; Xu, Z.; Cui, Y.; Jia, Y. *Angew. Chem., Int. Ed*. **2011**, *50*, 4447. m) Mascal, M.; Modes, K. V.; Durmus, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4445. n) Guo, L.; Zhang, Y.; Hu, W.; Li, L.; Jia, Y. *Chem. Commun*. **2014**, *50*, 3299. Dragmacidin E: o) Feldman, K. S.; Ngernmeesri, P. *Org. Lett*. **2005**, *7*, 5449. p) Feldman, K. S.; Ngernmeesri, P. *Org. Lett*. **2011**, *13*, 5704.

28) For other examples based on the stepwise construction of the target skeleton, see: a) Bur, S. K.; Padwa, A. *Org. Lett*. **2002**, *4*, 4135. b) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc*. **2006**, *128*, 4946. c) Huntley, R. J.; Funk, R. L. *Org. Lett*. **2006**, *8*, 4775. d) Lauchli, R.; Shea, K. J. *Org. Lett*. **2006**, *8*, 5287. e) Trost, B. M.; McDougall, P. J. *Org. Lett*. **2009**, *11*, 3782. f) Suetsugu, S.; Nishiguchi, H.; Tsukano, C.; Takemoto, Y. *Org. Lett*. **2014**, *16*, 996. g) Jiang, B.; Ye, Q.; Fan, W.; Wang, S.-L.; Tu, S.-J.; Li, G. *Chem. Commun*. **2014**, *50*, 6108.

29) For review, see: Gritsch, P. J.; Leitner, C.; Pfaffenbach, M.; Gaich, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 1208.

30) a) Park, I.-K.; Park, J.; Cho, C.-G. *Angew. Chem., Int. Ed*. **2012**, *51*, 2496. b) Park, J.; Kim, S.-Y.; Kim, J.-E.; Cho, C.-G. *Org. Lett*. **2014**, *16*, 178.

31) a) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. *J. Am. Chem. Soc*. **2013**, *135*, 1600. b) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed*. **2013**, 52, 4902.

32) Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc*. **2014**, *136*, 2272.

33) Nakano, S.; Inoue, N.; Hamada, Y.; Nemoto, T. *Org. Lett*. **2015**, *17*, 2622.

34) For other efficient methods for constructing 3,4-fused indole frameworks based on Rh-catalyzed C–H activation, see: a) Zhang, X.; Li, Y.; Shi, H.; Zhang, L.; Zhang, S.; Xu, X.; Liu, Q. *Chem. Commun*. **2014**, *50*, 7306; b) Tao, P.; Jia, Y. *Chem. Commun*. **2014**, *50*, 7367; c) Zhou, B.; Yang, Y.; Tang, H.; Du, J.; Feng, H.; Li, Y. *Org. Lett*. **2014**, *16*, 3900.

35) a) Mukai, C.; Takahashi, Y. *Org. Lett*. **2005**, *7*, 5793. b) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem*. **2004**, *69*, 2128. c) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed*. **2007**, *46*, 3931.

36) Gabbutt, C. D.; Mark Heron, B.; Instone, A. C.; Thomas, D. A.; Partington, S. M.; Hursthouse, M. B.; Gelbrich, T. *Euro. J. Org. Chem*. **2003**, 1220.

37) a) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. *J. Orgmet. Chem*. **1995**, *493*, 19C. b) Ogoshi, S.; Fukunishi, Y.; Tsutsumi, K.;Kurosawa, H. *J. Chem. Soc. Chem. Commun*. **1995**, 2485. c) Nishida, T.; Ogoshi, S.; Tsutsumi, K.; Fukunishi, Y.; Kurosawa, H. *Organometallics* **2000**, *19*, 4488. d) Ogoshi, S.; Nishida, T.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *J. Orgmet. Chem*. **2001**, *620*, 190. e) Kurosawa, H.; Ogoshi, S. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 973. f) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 2687.

38) a) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164. b) Graham, J. P.; Wojcicki, A. Bursten, B. E.; *Organometallics* **1999**, *18*, 837.

39) a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 9134. b) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 13210. c) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem.*

Soc. **2010**, *132*, 13949. d) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E., Morken, J. P. *Angew. Chem., Int. Ed*. **2012**, *51*, 521.

40) a) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Chem. Commun*. **2012**, *48*, 5431. b) Yokosaka, T.; Nakayama, H.; Nemoto, T.; Hamada, Y. *Org. Lett*. **2013**, *15*, 2978. c) Yokosaka, T.; Kanehira, T.; Nakayama, H.; Nemoto, T.; Hamada, Y. *Tetrahedron* **2014**, *70*, 2151.

41) Yokosaka, T.; Shiga, N.; Nemoto, T.; Hamada, Y. *J. Org. Chem.* **2014**, *79*, 3866.

42) For reviews on the synthesis of quinolines, see: a) Jones, G. Comprehensive Heterocyclic Chemistry, Katritzky, A. R., Rees, A. R., Eds.; Pergamon, New York, 1984; Vol. 2, Part 2A, p 395. b) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463.

43) Carroll, A. R.; Scheuer, P. J. *J. Org. Chem*. **1990**, *55*, 4426.

44) Pommier, Y. *Nature Reviews Cancer* **2006**, *6*, 789.

45) a) Fader, L. D.; Malenfant, M. P.; Carson, R, Bilodeau, F.; Landry, S.; Pesant, M.; Brochu, C.; Morin, S.; Chabot, C.; Halmos, T.; Bousquet, Y.; Bailey, M. D.; Kawai, S. H.; Coulombe, R.; LaPlante, S.; Jakalian, A.; Bhardwaj, P. K.; Wernic, D.; Schroeder, P.; Amad, M.; Edwards, P.; Garneau, M.; Duan, J.; Coedingley, M.; Bethell, R.; Mason, S. W.; Bos, M.; Bonneau, P.; Poupart, M.-A.; Faucher, A.-M.; Simoneau, B.; Fenwick, C.; Yoakim, C.; Tsantrizos, Y. *ACS Med. Chem. Lett*. **2014**, *5*, 422. b) Fendrick, K. R.; Li, W.; Zhang, Y.; Tang, W.; Gao, J.; Rodriguez, S.; Patel, N. D.; Reeves, D. C.; Wu, J.-P.; Sanyal, S.; GOnnella, N.; Qu, B.; Haddad, N.; Lorenz, J. C.; Sidhu, K.; Wang, J.; Ma, S.; Grinberg, N.; Lee, Heewon.; Trantrizos, Y.; Poupart, M.-A.; Busacca, C. A.; Yee, N. K.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem., Int. Ed*. **2015**, *54*, 7144.

46) a) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem*. **2001**, 66, 4635. b) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett*. **2004**, *6*, 2361. c) Huang, W.; Shen, Q.; Wang, J.; Zhou, X. *J. Org. Chem*. **2008**, *73*, 1586.

47) Liu, Z.; Liao, P.; Bi, X. *Chem. Eur. J*. **2014**, *20*, 17277.

48) Suzuki, Y.; Nemoto, T.; Kakugawa, K.; Hamajima, A.; Hamada, Y. *Org. Lett*. **2012**, *14*, 2350.

49) After published our paper, some related transition metal-catalyzed Friedel–Crafts type allylic alkylation of phenols were reported, see: a) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Org. Lett*. **2012**, *14*, 2579. b) Zhao, Z.-L.; Xu, Q.-L.; Gu,Q.; Wu, X.-Y. You, S.-L. *Org. Biomol. Chem*. **2015**, *13*, 3086.

50) Suzuki, Y.; Matsuo, N.; Nemoto, T.; Hamada, Y. *Tetrahedron*. **2013**, *69*, 5913.

51) Suzuki, Y.; Tanaka, Y.; Nakano, S.; Dodo, K.; Yoda, N.; Shinohara, K.; Kita, K.; Kaneda, A.; Sodeoka, M.; Hamada, Y.; Nemoto, T. *submitted.*

52) 根本哲宏，濱田康正，鈴木雄太，仲野駿一，田中唯人，井上直也　特願 2015-164962

53) Suzuki, Y.; Nemoto, T.; Nakano, S.; Zhao, Z.; Yoshimatsu, Y.; Hamada, Y. *Tetrahedron*. *Lett.* **2014**, *55*, 6726.

Experimental Section

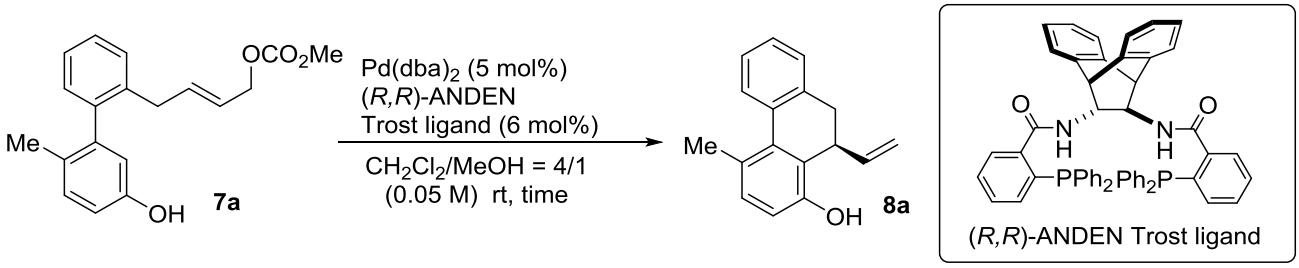
General

Infrared (IR) spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$, were reported downfield from TMS (= 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. JEOL ecp 600 spectrometer was used for the determination of the absolute configuration. EI mass spectra were measured on JEOL GCmate MS-BU20. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm; column, DAICEL CHIRALCEL OD-H, DAICEL CHIRALPAK AS-H, DAICEL CHIRALPAK AD-H, DAICEL CHIRALPAK OJ-H; mobile phase: hexane–2-propanol. Reactions were carried out in dry solvent under argon atmosphere. Other reagents were purified by the usual methods.

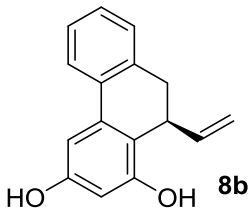
Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F254/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, cerium-phosphomolybdic acid, ninhydrin, and anisaldehyde solution followed by heating. Column chromatography was performed with silica gel 60 N (spherical, neutral 40-50 μm).

1. Synthesis of 9,10-dihydrophenanthrenes

1-1. General Procedure for the Pd-catalyzed Intramolecular Friedel–Crafts Allylic Alkylation of Phenols and Product Characterizations

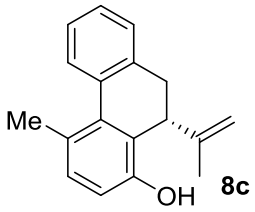


General Procedure: 8a (27.1 mg, 0.0868 mmol), $Pd(dba)_2$ (2.5 mg, 0.00434 mmol), and (*R*,*R*)-ANDEN-phenyl Trost Ligand (4.2 mg, 0.00521 mmol) were dissolved in CH_2Cl_2 (1.40 mL) and MeOH (0.35 mL) under argon atmosphere, and the resulting solution was stirred at room temperature. After 16 h, the reaction was quenched with sat. aq. NH_4Cl, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 20/1) to give **15a** (20.0 mg, 97% yield) as a colorless oil. IR (ATR) ν 3417, 2930, 1464, 1448, 1290, 1264, 1192, 1125, 1076, 913, 890, 807, 782, 757, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.57 (s, 3H), 2.84 (dd, *J* = 2.0 Hz, 14.4 Hz, 1H), 3.07 (dd, *J* = 5.6 Hz, 14.4 Hz, 1H), 3.89–3.93 (m, 1H), 4.64 (s, 1H), 4.85–4.93 (m, 2H), 5.68 (ddd, *J* = 2.8 Hz, 10.4 Hz, 16.8 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.21–7.29 (m, 3H), 7.63 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.5, 35.1, 36.3, 114.6, 115.3, 125.9, 126.2, 126.9, 127.1, 127.9, 128.5, 131.0, 134.5, 135.0, 136.4, 137.9, 150.5; (+)-ESI-LRMS *m/z* 257 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{17}H_{14}NaO$ ($M+Na^+$): 257.0942. Found: 257.0900; $[\alpha]_D^{14}$ +200.9 (*c* 1.17, $CHCl_3$, 91% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 24.0 min [(*R*)-(–)-isomer] and 27.8 min [(*S*)-(+)-isomer], detection at 254 nm).



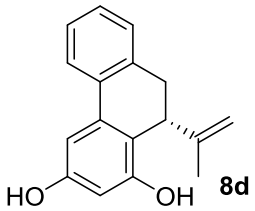
Compound 8b: pale yellow oil; IR (ATR) ν 3347, 1690, 1573, 1446, 1340, 1259, 1160, 1121, 1072, 1005, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.89 (dd, *J* = 2.4 Hz, 15.2 Hz, 1H), 3.13 (dd, *J* = 6.4 Hz, 15.2 Hz, 1H), 3.76–3.85 (m, 1H), 4.88–4.93 (m, 2H), 5.12 (s, 1H), 5.14 (s, 1H), 5.76 (ddd, *J* = 7.2 Hz, 10.0 Hz, 16.8 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 7.20–7.28 (m, 3H), 7.61–7.63 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 35.4, 34.9, 102.6, 103.8, 114.9, 116.9, 123.8, 126.9, 127.9, 128.8, 133.5, 134.7, 136.3, 138.9, 153.9, 155.2; (+)-ESI-LRMS *m/z* 261 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{16}H_{14}NaO_2$ ($M+Na^+$): 261.0891. Found: 261.0884; $[\alpha]_D^{13}$ +130.6 (*c* 1.35,

$CHCl_3$, 90% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow rate: 1.0 mL/min, t_R 17.5 min [(–)-isomer] and 41.0 min [(+)-isomer], detection at 254 nm).



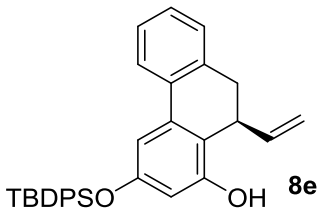
8c

Compound 8c: colorless oil; IR (ATR) ν 3420, 2948, 1588, 1569, 1465, 1447, 1291, 1265, 1190, 1124, 1079, 896, 809, 789, 755, 736 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66 (s, 3H), 2.57 (s, 3H), 2.99 (d, J = 4.0 Hz, 2H), 3.78 (t, J = 4.0 Hz, 1H), 4.36 (s, 1H), 4.64 (s, 1H), 4.72 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.19–7.28 (m, 2H), 7.61 (d, J = 7.2 Hz, 1H); ^{13}C NMR (CD_3OD): δ 21.0, 22.4, 33.7, 39.7, 112.8, 114.7, 126.0, 126.7, 126.9, 127.0, 127.8, 128.2, 131.0, 134.7, 135.5, 136.4, 144.4, 150.7; EI-LRMS *m/z* 250 (M^+); EI-HRMS. Calcd for $C_{16}H_{18}O$ (M^+): 250.1358. Found: 250.1356; $[\alpha]_D^{13}$ –140.8 (*c* 0.62, $CHCl_3$, 93% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 17.6 min [(–)-isomer] and 25.1 min [(+)-isomer], detection at 254 nm).



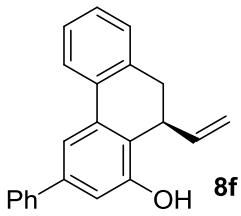
8d

Compound 8d: colorless oil; IR (ATR) ν 3339, 2941, 1608, 1573, 1445, 1338, 1266, 1213, 1158, 1120, 1074, 1004, 777, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66 (s, 3H), 3.02 (dd, J = 2.0 Hz, 15.6 Hz, 1H), 3.12 (dd, J = 6.8 Hz, 15.6 Hz, 1H), 3.70–3.75 (m, 1H), 4.49 (s, 1H), 4.69 (s, 1H), 4.83 (s, 1H), 5.00 (s, 1H), 6.35–6.36 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 7.18–7.29 (m, 3H), 7.63 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.9, 33.2, 38.3, 102.7, 103.7, 112.4, 117.2, 123.7, 126.9, 127.8, 128.4, 133.7, 134.9, 136.7, 145.9, 154.1, 155.2; (+)-ESI-LRMS *m/z* 275 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{17}H_{16}NaO_2$ ($M+Na^+$): 275.1048. Found: 275.1009; $[\alpha]_D^{14}$ –133.6 (*c* 1.34, $CHCl_3$, 91% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 80/20, flow rate: 0.5 mL/min, t_R 14.4 min [(+)-isomer] and 26.3 min [(–)-isomer], detection at 254 nm).



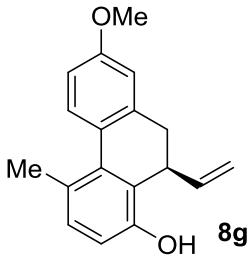
8e

Compound 8e: colorless oil; IR (ATR) ν 3545, 2930, 1613, 1570, 1426, 1342, 1178, 1114, 1022, 753, 701 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s, 9H), 2.83 (dd, *J* = 1.8 Hz, 15.4 Hz, 1H), 3.12 (dd, *J* = 5.6 Hz, 15.4 Hz, 1H), 3.76–3.79 (m, 1H), 4.66 (s, 1H), 4.82–4.87 (m, 2H), 5.69–5.78 (m, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 7.12–7.26 (m, 5H), 7.36–7.46 (m, 6H), 7.74–7.78 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 19.5, 26.5, 34.4, 34.9, 106.7, 108.4, 114.6, 117.1, 123.8, 126.7, 127.5, 127.8 (4C), 128.6, 129.9 (2C), 133.0, 133.8, 134.6, 135.5 (2C), 135.6 (4C), 139.0, 153.3, 155.3; (–)-ESI-LRMS *m/z* 475 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{32}H_{31}O_2Si$ ($[M–H]^-$): 475.2093. Found: 475.2056; $[\alpha]_D^{20}$ +84.4 (*c* 1.24, $CHCl_3$, 92% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 11.2 min [(+)-isomer] and 12.2 min [(–)-isomer], detection at 254 nm).



8f

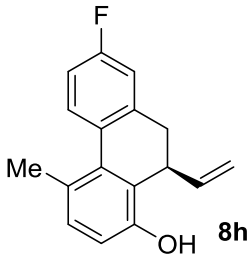
Compound 8f: colorless oil; IR (ATR) ν 3530, 1567, 1405, 1260, 1186, 1074, 910, 781, 761, 729, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.94 (dd, *J* = 1.8 Hz, 15.2 Hz, 1H), 3.20 (dd, *J* = 6.2 Hz, 15.2 Hz, 1H), 3.95–3.98 (m, 1H), 4.92–5.01 (m, 3H), 5.84 (ddd, *J* = 6.8 Hz, 10.2 Hz, 17.0 Hz, 1H), 7.00 (d, *J* = 0.8 Hz, 1H), 7.22–7.37 (m, 4H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.61–7.64 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 34.3, 35.2, 113.8, 115.2, 115.9, 123.3, 123.9, 127.0 (2C), 127.4, 127.8, 128.8 (2C), 128.9, 133.9, 134.6, 135.7, 138.4, 140.9, 141.2, 153.2; (–)-ESI-LRMS *m/z* 297 ($[M–H]^-$); (–)-EI-HRMS. Calcd for $C_{22}H_{17}O$ ($[M–H]^-$): 297.1279. Found: 297.1266; $[\alpha]_D^{21}$ +205.0 (*c* 0.53, $CHCl_3$, 94% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 27.2 min [(–)-isomer] and 37.9 min [(+)-isomer], detection at 254 nm).



8g

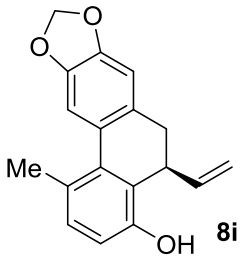
Compound 8g: colorless oil; IR (ATR) ν 3419, 2935, 1463, 1288, 1244, 1159, 1072, 1039, 912, 889, 804, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H), 2.77 (dd, *J* = 1.8, 14.8 Hz, 1H), 3.05 (dd, *J* = 5.4, 14.8 Hz, 1H), 3.83 (s, 3H), 3.87–3.94 (m, 1H), 4.84–4.95 (m, 3H), 5.68 (ddd, *J* = 6.6, 10.2, 17.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.77–6.83 (m, 2H), 7.01–7.06 (m, 1H), 7.54–7.59 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 22.5, 35.5, 36.2, 55.1, 110.9, 113.8, 114.1, 115.2, 125.5, 126.4, 127.4, 129.1, 130.9, 134.8, 138.0, 138.3, 150.6, 158.3; (–)-ESI-LRMS *m/z* 265 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{18}H_{17}O_2$ ($[M–H]^-$): 265.1229. Found: 265.1233; $[\alpha]_D^{22}$ +138.7 (*c* 2.08, $CHCl_3$, 94% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H,

hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 26.5 min [(–)-isomer] and 40.0 min [(+)-isomer], detection at 254 nm).



8h

Compound 8h: colorless oil; IR (ATR) ν 3422, 2947, 1464, 1283, 1243, 1226, 1148, 917, 868, 806 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H), 2.80 (dd, *J* = 2.4, 14.8 Hz, 1H), 3.04 (dd, *J* = 5.6, 14.8 Hz, 1H), 3.90–3.95 (m, 1H), 4.75 (br-s, 1H), 4.83–4.94 (m, 2H), 5.66 (ddd, *J* = 6.4, 10.4, 16.8 Hz, 1H), 6.68–6.73 (m, 1H), 6.91–6.99 (m, 2H), 7.04–7.10 (m, 1H), 7.54–7.62 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 22.4, 35.2, 36.0, 112.6 (d, *J* = 21.0 Hz), 114.5, 115.3 (d, *J* = 20.9 Hz), 115.5, 125.8, 126.7, 129.4 (d, *J* = 8.6 Hz), 130.6 (d, *J* = 2.9 Hz), 131.1, 134.3, 137.5, 139.1 (d, *J* = 7.6 Hz), 150.5, 161.5 (d, *J* = 246.0 Hz); (–)-ESI-LRMS *m/z* 253 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{17}H_{14}FO$ ($[M–H]^-$): 253.1029. Found: 253.1044; $[\alpha]_D^{22}$ +148.6 (*c* 1.31, $CHCl_3$, 94% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, t_R 20.8 min [(+)-isomer] and 22.2 min [(–)-isomer], detection at 254 nm).

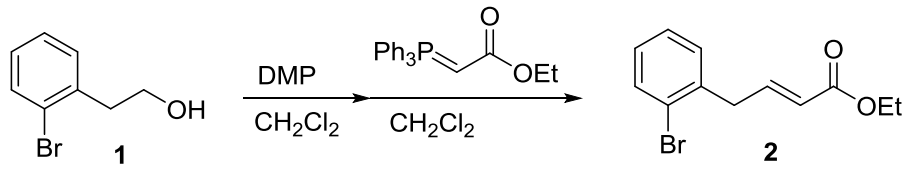


8i

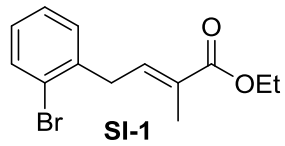
Compound 15i: colorless oil; IR (ATR) ν 3502, 2895, 1503, 1468, 1244, 1218, 1038, 935, 808, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H), 2.73 (dd, *J* = 2.2 Hz, 14.8 Hz, 1H), 2.98 (dd, *J* = 5.6 Hz, 14.8 Hz, 1H), 3.83–3.87 (m, 1H), 4.70 (br–s, 1H), 4.88–4.94 (m, 2H), 5.70 (ddd, *J* = 2.8 Hz, 10.4 Hz, 16.8 Hz, 1H), 5.96 (s, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.6, 35.2, 36.3, 100.9, 108.6, 109.0, 114.1, 115.3, 125.6, 126.4, 128.0, 130.7, 131.1, 135.1, 137.8, 145.7, 146.1, 150.5; ESI-LRMS *m/z* 279 ($[M–H]^-$); ESI-HRMS. Calcd for $C_{18}H_{15}O_3$ ($[M–H]^-$): 279.1021. Found: 279.1016; $[\alpha]_D^{21}$ +69.7 (*c* 1.015, $CHCl_3$, 87% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 90/10, flow rate: 0.5 mL/min, t_R 17.9 min [(–)-isomer] and 24.6 min [(+)-isomer], detection at 254 nm).

1-2. Substrate Syntheses and Compound Characterizations

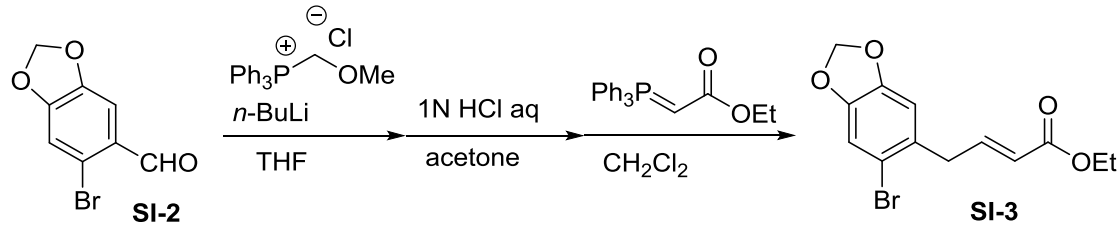
1-2-1. General Procedure for the Synthesis of the Northern Fragment.



To a stirred solution of Dess-Martin periodinane (13.2 g, 31.0 mmol) in CH_2Cl_2 (200 mL) at room temperature was added a CH_2Cl_2 solution of commercially available alcohol **8** (5.2g, 25.9 mmol in 60 mL of CH_2Cl_2), and the resulting solution was kept stirring for 1 h at the same temperature. The reaction mixture was diluted with Et_2O, and quenched with 1N aq. NaOH. After separation of the aqueous layer, the organic layer was washed with brine, and dried over Na_2SO_4, and then evaporated *in vacuo*. The obtained crude residue was used for the next reaction without purification because of instability of the product. To a stirred solution of the crude residue in CH_2Cl_2 (500 mL) at room temperature was added a Wittig reagent (13.0 g, 37.3 mmol), and the resulting mixture was stirred for 2 h at the same temperature. After evaporation of the solvent, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 20/1) to give **9** (5.66 g, 81% yield) as a colorless oil. IR (ATR) ν 2980, 1713, 1653, 1266, 1194, 1155, 1024, 981, 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.66 (dd, *J* = 1.8 Hz, 6.4 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.77 (dt, *J* = 15.6 Hz, 1.8 Hz, 1H), 7.07 (dt, *J* = 15.6 Hz, 5.4 Hz, 1H), 7.09–7.14 (m, 1H), 7.19–7.21 (m, 1H), 7.25–7.29 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.5, 60.3, 122.8, 124.5, 127.7, 128.4, 130.7, 132.9, 137.3, 145.4, 166.3; (+)-ESI-LRMS *m/z* 291 ($M+Na^+$), 293 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{12}H_{13}BrNaO_2$ ($M+Na^+$): 290.9997. Found: 290.9996.
Reference for **Compound SI-1**: *J. Org. Chem.* **2010**, *75*, 5289.



Compound SI-1: This compound was prepared from **1**. Colorless oil; IR (ATR) ν 2980, 1704, 1469, 1440, 1248, 1178, 1126, 1068, 1024, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.97 (d, *J* = 1.2 Hz, 3H), 3.63 (d, *J* = 7.6 Hz, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 6.84 (tq, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.07–7.11 (m, 1H), 7.19–7.27 (m, 2H), 7.54–7.56 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.2, 35.3, 60.5, 124.4, 127.6, 128.1, 129.1, 130.2, 132.8, 138.3, 138.4, 167.8; EI-LRMS *m/z* 282 (M^+), 284 (M^++2); EI-HRMS. Calcd for $C_{13}H_{15}BrO_2$ (M^+): 282.0255. Found: 282.0213.

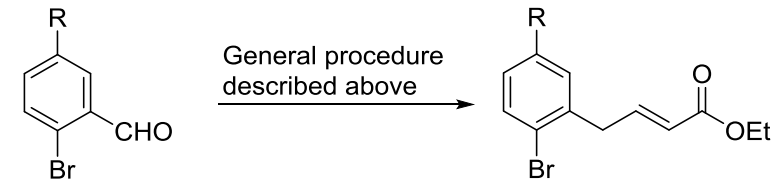


Compound SI-2: Commercially Available.

Compound SI-3: To a stirred solution of (methoxymethyl)triphenyl phosphonium chloride (2.23 g, 6.5 mmol) in THF (25 mL) was added *n*-BuLi (3.7 mL, 1.56 M solution in hexane, 5.75 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. A solution of 2-bromopiperonal **SI–2** (1.15 g, 5.0 mmol) in THF (5 mL) was added to the reaction, and then the resulting mixture was stirred at room temperature. After 30 min, the reaction was quenched with water, and diluted with AcOEt. After separation of the aqueous layer, the organic layer was washed with brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The obtained crude methyl vinyl ether derivative was used for the next step without purification.

To a stirred solution of the crude methyl vinyl ether derivative in acetone (10 mL) was added an aqueous solution of 1N aq. HCl (10 mL) at room temperature. The resulting solution was refluxed for 3 h. After evaporation of the organic solvent *in vacuo*, water was added to the mixture, and the resulting slurry was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*. The obtained crude aldehyde was used for the next reaction without purification because of instability of this product.

To a stirred solution of crude aldehyde in CH_2Cl_2 (5 mL) at room temperature was added a Wittig reagent (2.6 g, 7.5 mmol), and the resulting mixture was stirred for 2 h at the same temperature. After evaporation of the solvent, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 30/1) to give **SI-5** (1.02 g, 65% yield over 3 steps) as a colorless oil. IR (ATR) ν 2980, 1712, 1475, 1268, 1228, 1157, 1113, 1034, 982, 929, 858 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 3.55 (dd, *J* = 1.8 Hz, 6.4 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 5.75 (td, *J* = 1.8 Hz, 15.6 Hz, 1H), 5.96 (s, 2H), 6.67 (s, 1H), 7.00 (s, 1H), 7.01 (td, *J* = 6.4 Hz, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.4, 60.3, 101.7, 110.2, 112.8, 114.6, 122.6, 130.1, 145.5, 147.3, 147.5, 166.3; (+)-ESI-LRMS *m/z* 335 ($M+Na^+$), 337 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{13}H_{13}BrNaO_4$ ($M+Na^+$): 334.9895. Found: 334.9926.



SI-4 (R = MeO)
SI-6 (R = F)

SI-5 (R = MeO)
SI-7 (R = F)

Compound SI-4: Commercially Available.

Compound SI-5: Colorless oil; IR (ATR) ν 2979, 1713, 1472, 1267, 1239, 1199, 1131, 1040, 1016, 983, 803 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.60 (dd, *J* = 2.0 Hz, 6.4 Hz, 2H), 3.77 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.78 (dt, *J* = 15.6 Hz, 2.0 Hz, 1H), 6.68 (dd, *J* = 3.2 Hz, 8.8 Hz, 1H), 6.72–6.76 (m, 1H), 7.05 (dt, *J* = 15.6 Hz,

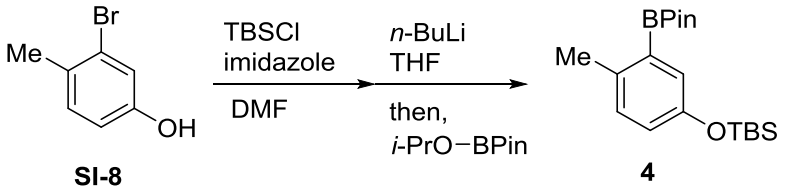
6.4 Hz, 1H), 7.41–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.7, 55.4, 60.3, 113.9, 114.9, 116.4, 122.9, 133.4, 138.2, 145.2, 159.1, 166.3; (+)-ESI-LRMS *m/z* 321 ($M+Na^+$), 323 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{13}H_{15}BrNaO_3$ ($M+Na^+$): 321.0102. Found: 321.0114.

Compound SI-6: Commercially Available.

Compound SI-7: Colorless oil; IR (ATR) ν 2981, 1715, 1469, 1268, 1234, 1198, 1155, 1031, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.62 (dd, *J* = 1.6 Hz, 6.4 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.79 (dd, *J* = 1.6 Hz, 15.6 Hz, 1H), 6.82–6.90 (m, 1H), 6.91–6.97 (m, 1H), 7.04 (dt, *J* = 15.6 Hz, 6.4 Hz, 1H), 7.50–7.54 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.5, 60.4, 115.6 (d, *J* = 22.9 Hz), 117.6 (d, *J* = 22.9 Hz), 118.6 (d, *J* = 3.8 Hz), 123.4, 134.1 (d, *J* = 8.6 Hz), 139.4 (d, *J* = 7.6 Hz), 144.3, 162.0 (d, *J* = 246.0 Hz), 166.1; EI-LRMS *m/z* 286 (M^+), 288 (M^++2); EI-HRMS. Calcd for $C_{12}H_{12}BrFO_2$ (M^+): 286.0005. Found: 286.0004.

1-2-2. General Procedure for the Synthesis of the Southern Fragment.

Southern fragments were prepared from the corresponding aryl bromides.

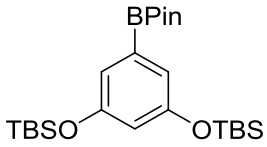


SI-8 **4**

Compound 4: To a stirred solution of phenol derivative **SI-8** (4.58 g, 24.5 mmol) and imidazole (3.34 g, 49.0 mmol) in DMF (24.5 mL) at 0 °C was added TBSCl (5.54 g, 36.8 mmol), and the resulting mixture was stirred for 2 h at room temperature. After dilution with Et_2O, the mixture was washed with water (2 times), brine, and then dried over Na_2SO_4. After concentration *in vacuo*, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 200/1) to give silylated phenol (5.63 g, 76% yield) as a colorless oil.

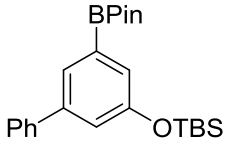
To a stirred solution of silylated phenol (5.63 g, 18.7 mmol) in THF (93.5 mL) at –78 °C was added a hexane solution of *n*-BuLi (14.4 mL, 1.56 M solution in hexane, 22.4 mmol). After the reaction mixture was stirred for 30 min at the same temperature, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.60 mL, 22.4 mmol) was added to the reaction. After being stirred for 4 h at –78 °C, the reaction was quenched with water, and diluted with AcOEt. The mixture was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 100/1) to give **4** (4.89 g, 75% yield) as white solids. Mp: 29–30 °C; IR (ATR) ν 2954, 2925, 2853, 1405, 1334, 1301, 1233, 1144, 944, 838, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.18 (s, 6H), 0.98 (s, 9H), 1.33 (s, 12H), 2.45 (s, 3H), 6.78 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ –4.4 (2C), 18.2, 21.3, 24.8 (4C), 25.7 (3C), 83.4 (2C), 122.1, 126.9, 130.7, 137.2, 152.7; EI-LRMS *m/z* 348 (M^+); EI-HRMS. Calcd for $C_{19}H_{33}BO_3Si$ (M^+): 348.2292. Found: 348.2293.

Compound SI-8: Commercially Available



SI-9

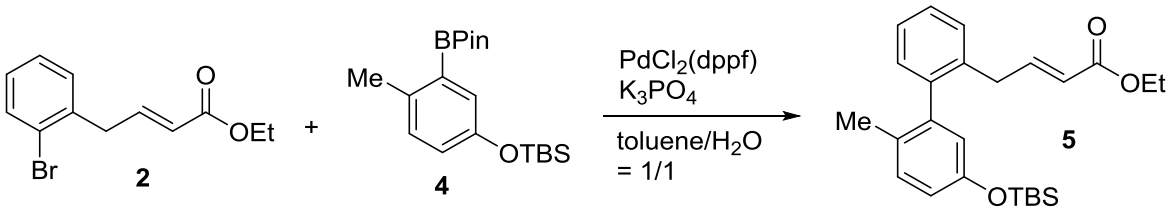
Compound SI-9 was prepared from the corresponding phenol derivative (*Synthesis* **2010**, 1512.) according to the general procedure described above. White solid; Mp: 139–140 °C; IR (ATR) ν 2931, 2859, 1577, 1429, 1368, 1174, 1144, 973, 833, 779 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.19 (s, 12 H), 0.98 (s, 18 H), 1.32 (s, 12 H), 6.42 (t, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ –4.4 (4C), 18.2 (2C), 24.8 (4C), 25.7 (6C), 83.7 (2C), 114.8, 119.3 (2C), 119.3, 156.0 (2C); (+)-ESI-LRMS *m/z* 465 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{46}BO_4Si_2$ ($M+H^+$): 465.3028. Found: 465.2989.



SI-10

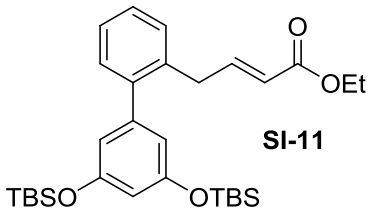
Compound SI-10 was prepared from the corresponding phenol derivative (*J. Med. Chem.* **2009**, 52, 2036.) according to the general procedure described above. White solid; Mp. 75–75.5 °C; IR (ATR) ν 2930, 1556, 1370, 1345, 1142, 973, 835, 701 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.23 (s, 6 H), 1.01 (s, 9 H), 1.35 (s, 12 H), 7.15 (t, *J* = 2.2 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$): δ –4.3 (2C), 18.2, 24.87 (4C), 25.6 (3C), 83.8 (4C), 121.6, 125.0, 126.6, 127.2 (3C), 128.6 (3C), 140.9, 142.1, 155.5; (+)-ESI-LRMS *m/z* 411 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{36}BO_3Si$ ($M+H^+$): 411.2527. Found: 411.2535.

1-2-3. General Procedure for the Suzuki-Miyaura Cross Coupling.



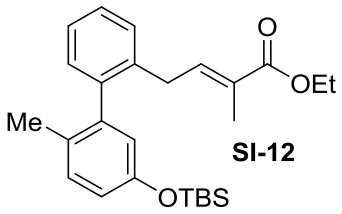
A mixture of **2** (270 mg, 1.00 mmol), **4** (453 mg, 1.30 mmol), $PdCl_2$(dppf) (29.5 mg, 0.05 mmol), and K_3PO_4 (637 mg, 3.00 mmol) in toluene (5 mL) and H_2O (5 mL) was stirred for 24 h at 90 °C. After the reaction was quenched with water, AcOEt was added to the mixture. The aqueous layer was separated and the resulting organic layer was washed with brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 30/1) to give **5** (390 mg, 95% yield) as a colorless oil. IR (ATR) ν 2929, 1719, 1482, 1305, 1261, 1212, 1155, 936, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.96 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.94 (s, 3H), 3.23 (ddd, *J* = 1.8 Hz, 6.4 Hz, 16.0 Hz, 1H), 3.33 (ddd, *J* = 1.8 Hz, 7.2 Hz, 16.0 Hz,

1H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.59 (ddd, *J* = 1.8 Hz, 1.8 Hz, 15.6 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.91 (ddd, *J* = 6.4 Hz, 7.2 Hz, 15.6 Hz, 1H), 7.08–71.4 (m, 2H), 7.22–7.34 (m, 3H); ^{13}C NMR ($CDCl_3$): δ –4.5 (2C), 14.2, 18.2, 19.1, 25.6 (3C), 35.7, 60.1, 119.2, 121.0, 122.1, 126.6, 127.5, 128.5, 129.5, 129.7, 130.7, 135.4, 141.4, 141.5, 147.2, 153.2, 166.4; (+)-ESI-LRMS *m/z* 433 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{25}H_{34}NaO_3Si$ ($M+Na^+$): 433.2175. Found: 433.2147.



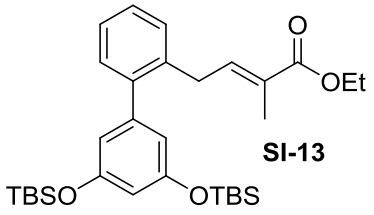
SI-11

Compound SI-11 was prepared from **2** and **SI-9** according to the general procedure described above. Colorless oil; IR (ATR) ν 2930, 1720, 1584, 1425, 1348, 1254, 1160, 1027, 928, 829, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.19 (s, 12H), 0.97 (s, 18H), 1.25 (t, *J* = 6.8 Hz, 3H), 3.49 (dd, *J* = 1.6 Hz, 6.4 Hz, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 5.65 (td, *J* = 1.6 Hz, 15.6 Hz, 1H), 6.34 (t, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 2H), 7.03 (td, *J* = 6.4 Hz, 15.6 Hz, 1H), 7.20–7.33 (m, 4H); ^{13}C NMR ($CDCl_3$): δ –4.4 (4C), 14.2, 18.2, 25.6 (6C), 35.8, 60.1, 111.1, 114.4, 122.3, 126.6, 127.6, 129.9, 130.0, 134.9, 142.0, 142.8, 148.0, 156.2 (2C), 166.4; (+)-ESI-LRMS *m/z* 549 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{30}H_{46}NaO_4Si_2$ ($M+Na^+$): 549.2832. Found: 549.2786.



SI-12

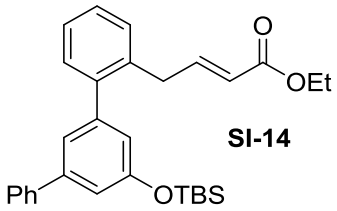
Compound SI-12 was prepared from **SI-1** and **4** according to the general procedure described above. Colorless oil; IR (ATR) ν 2929, 1709, 1481, 1250, 1211, 1120, 932, 837, 779, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.18 (d, *J* = 1.4 Hz, 6H), 0.97 (d, *J* = 1.4 Hz, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.65 (s, 3H), 1.95 (s, 3H), 3.24 (dd, *J* = 7.6 Hz, 15.6 Hz, 1H), 3.33 (dd, *J* = 7.6 Hz, 15.6 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 6.63 (d, *J* = 2.6 Hz, 1H), 6.70–6.77 (m, 2H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR ($CDCl_3$): δ –4.5 (2C), 12.1, 14.2, 18.1, 19.1, 25.6 (3C), 32.5, 60.3, 119.0, 121.0, 126.3, 127.6, 127.9, 128.6, 129.1, 129.6, 130.7, 136.8, 140.0, 141.3, 141.7, 153.2, 167.9; (+)-ESI-LRMS *m/z* 447 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{26}H_{36}NaO_3Si$ ($M+Na^+$): 447.2331. Found: 447.2354.



SI-13

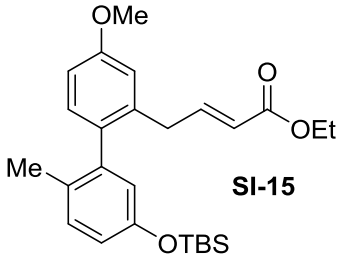
Compound SI-13 was prepared from **SI-1** and **SI-9** according to the general procedure described above. Colorless

oil; IR (ATR) ν 2929, 1712, 1583, 1424, 1348, 1251, 1160, 1026, 924, 828, 779, 739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.20 (s, 12H), 0.98 (s, 18H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.78 (s, 3H), 3.48 (d, *J* = 7.6 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.34–6.35 (m, 1H), 6.40 (m, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 7.21–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$): δ –4.4 (4C), 12.4, 14.2, 18.2, 25.6 (6C), 32.6, 60.4, 110.9, 114.5 (2C), 126.3, 127.6, 128.0, 129.3, 129.8, 136.6, 140.6, 141.8, 143.0, 156.2 (2C), 167.9; (+)-ESI-LRMS *m/z* 563 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{31}H_{48}NaO_4Si_2$ ($M+Na^+$): 563.2989. Found: 563.2951.



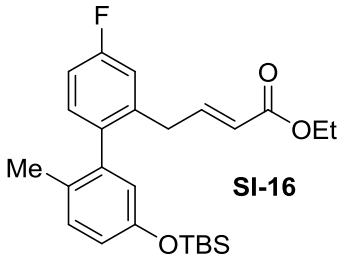
SI-14

Compound SI-14 was prepared from **2** and **SI-10** according to the general procedure described above. Colorless oil; IR (ATR) ν 2929, 1717, 1588, 1414, 1344, 1260, 1200, 956, 830, 781, 761, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.23 (s, 6H), 1.01 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 3.53 (dd, *J* = 1.8 Hz, 6.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.66 (td, *J* = 1.8 Hz, 15.6 Hz, 1H), 6.75 (t, *J* = 1.2 Hz, 1H), 7.04 (td, *J* = 6.4 Hz, 15.6 Hz, 1H), 7.07 (t, *J* = 1.2 Hz, 1H), 7.11 (t, *J* = 1.2 Hz, 1H), 7.24–7.36 (m, 5H), 7.40–7.44 (m, 2H), 7.57–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$): δ –4.4 (2C), 14.2, 18.2, 25.7 (3C), 36.0, 60.2, 117.7, 119.6, 121.2, 122.3, 126.7, 127.1 (2C), 127.5, 127.8, 128.7 (2C), 130.0, 130.1, 135.0, 140.6, 142.0, 142.4, 142.8, 147.8, 155.7, 166.4; (+)-ESI-LRMS *m/z* 495 ($M+Na^+$); (+)-EI-HRMS. Calcd for $C_{30}H_{36}NaO_3Si$ ($M+Na^+$): 495.2331. Found: 495.2293.



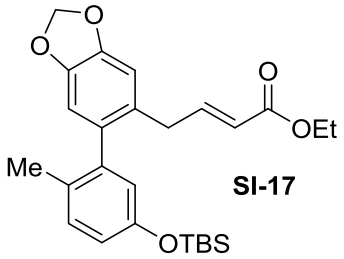
SI-15

Compound SI-15 was prepared from **SI-5** and **4** according to the general procedure described above. Colorless oil; IR (ATR) ν 2929, 1718, 1606, 1485, 1296, 1260, 1211, 1157, 1044, 943, 836, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.96 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.95 (s, 3H), 3.21 (ddd, *J* = 1.6 Hz, 6.6 Hz, 16.0 Hz, 1H), 3.30 (ddd, *J* = 1.2 Hz, 6.6 Hz, 16.0 Hz, 1H), 3.83 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 2H), 5.61 (dt, *J* = 15.6 Hz, 1.6 Hz, 1H), 6.57–6.61 (m, 1H), 6.71–6.85 (m, 3H), 6.91 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H), 6.85–6.94 (m, 2H); ^{13}C NMR ($CDCl_3$): δ –4.5 (2C), 14.2, 18.2, 19.1, 25.6 (2C), 35.9, 55.2, 60.1, 111.8, 114.9, 119.1, 121.5, 122.2, 129.0, 130.6, 130.7, 133.9, 136.7, 141.2, 147.0, 153.2, 158.8, 166.3; (+)-ESI-LRMS *m/z* 463 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{26}H_{36}NaO_4Si$ ($M+Na^+$): 463.2281. Found: 463.2257.



SI-16

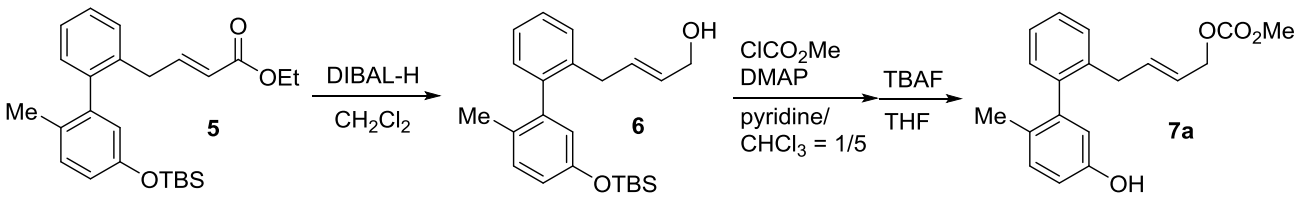
Compound SI-16 was prepared from **SI-7** and **4** according to the general procedure described above. Colorless oil; IR (ATR) ν 2929, 1719, 1484, 1303, 1260, 1227, 1191, 1155, 932, 836, 780, 688 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.93 (s, 3H), 3.17–3.26 (m, 1H), 3.26–3.34 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.62 (dt, *J* = 15.6 Hz, 1.2 Hz, 1H), 6.55–6.59 (m, 1H), 6.76 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 6.89 (dt, *J* = 15.6 Hz, 6.8 Hz, 1H), 6.93–7.01 (m, 2H), 7.06–7.12 (m, 2H); ^{13}C NMR ($CDCl_3$): δ –4.5 (2C), 14.2, 18.2, 19.0, 25.6 (3C), 35.6, 60.2, 113.6 (d, *J* = 21.0 Hz), 116.0 (d, *J* = 21.0 Hz), 119.4, 121.2, 122.7, 128.6, 130.9, 131.2 (d, *J* = 7.7 Hz), 137.2 (d, *J* = 3.8 Hz), 137.7 (d, *J* = 7.6 Hz), 140.5, 146.2, 153.3, 162.0 (d, *J* = 245.0 Hz), 166.2; ESI-LRMS *m/z* 451 ($M+Na^+$); ESI-HRMS. Calcd for $C_{25}H_{33}FNaO_3Si$ ($M+Na^+$): 451.2081. Found: 451.2047.



SI-17

Compound SI-17 was prepared from **SI-3** and **4** according to the general procedure described above. Colorless oil; IR (ATR) ν 2929, 1718, 1501, 1480, 1292, 1246, 1184, 1039, 925, 840, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.16 (s, 6H), 0.96 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.96 (s, 3H), 3.12 (ddd, *J* = 1.6 Hz, 6.4 Hz, 16.4 Hz, 1H), 3.22 (ddd, *J* = 1.6 Hz, 6.4 Hz, 16.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.60 (ddd, *J* = 1.6 Hz, 1.6 Hz, 15.4 Hz, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 5.98 (d, *J* = 1.4 Hz, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 6.60 (s, 1H), 6.71 (s, 1H), 6.74 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 6.88 (ddd, *J* = 6.4 Hz, 6.4 Hz, 15.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ –4.5 (2C), 14.2, 18.2, 19.0, 25.6 (3C), 35.5, 60.1, 101.1, 109.4, 109.7, 119.2, 121.3, 122.0, 128.5, 128.8, 130.8, 134.6, 141.2, 146.1, 146.9, 147.4, 153.2, 166.4; (+)-ESI-LRMS *m/z* 477 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{26}H_{34}NaO_5Si$ ($M+Na^+$): 477.2073. Found: 477.2037.

1-2-4. Experimental Procedure for the Preparation of Substrates 14a-14i.

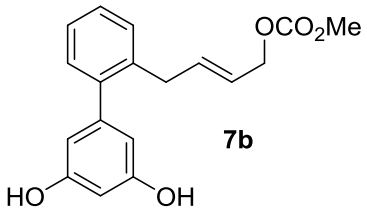


Compound 6: To a stirred solution of **5** (235 mg, 0.572 mmol) in CH_2Cl_2 (5.7 mL) at –78 °C was added DIBAL-H

(1.43 mL, 1M solution in hexane, 1.43 mmol). After the solution was stirred for 2.5 h at –78 °C, and 30 min at room temperature, the reaction was quenched by the addition of aq. 1M Rochelle salt. After being stirred for 1 h, the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 10/1) to give **6** (202 mg, 96% yield) as a colorless oil. IR (ATR) ν 2929, 1481, 1257, 1210, 969, 933, 837, 779, 737, 689 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.17 (s, 6H), 0.97 (s, 9H), 1.16 (t, *J* = 6.0 Hz, 1H), 1.95 (s, 3H), 3.10 (dd, *J* = 6.4 Hz, 15.2 Hz, 1H), 3.19 (dd, *J* = 6.4 Hz, 15.2 Hz, 1H), 4.02 (dd, *J* = 6.0 Hz, 6.0 Hz, 1H), 5.42 (dd, *J* = 6.0 Hz, 15.2 Hz, 1H), 5.64 (dd, *J* = 6.4 Hz, 15.2 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.75 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 7.08–7.11 (m, 2H), 7.22–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$): δ –4.5, 18.1, 19.1, 25.6 (3C), 35.9, 63.4, 118.9, 121.2, 126.0, 127.3, 128.5, 129.2, 129.5, 130.1, 130.5, 131.1, 137.5, 141.1, 141.9, 153.0; (+)-ESI-LRMS *m/z* 391 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{23}H_{32}NaO_2Si$ ($M+Na^+$): 391.2069. Found: 391.2066.

Compound 7a: To a stirred solution of **6** (227 mg, 0.616 mmol) and DMAP (15.0 mg, 0.123 mmol) in $CHCl_3$ (1 mL) and pyridine (0.2 mL) at 0 °C was added methyl chloroformate (0.120 mL, 1.54 mmol), and the resulting mixture was kept stirring for 3 h at room temperature. The reaction was quenched with 1N HCl at 0 °C, and then the resulting mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a stirred solution of the crude sample in THF (3.0 mL) at 0 °C was added TBAF (0.73 mL, 1M solution in THF, 0.73 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with AcOEt. The obtained mixture was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **7a** (180 mg, 95% yield) as a colorless oil. IR (ATR) ν 3416, 3021, 2955, 1745, 1720, 1442, 1258, 935, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.95 (s, 3H), 3.07 (dd, *J* = 2.8 Hz, 15.6 Hz, 1H), 3.18 (dd, *J* = 1.6 Hz, 16.0 Hz, 1H), 3.78 (s, 3H), 4.49–4.57 (m, 2H), 5.21 (d, *J* = 4.0 Hz, 1H), 5.24–5.31 (m, 1H), 5.76–5.83 (m, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 6.77 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 7.10–7.13 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 19.0, 36.0, 54.9, 68.4, 114.4, 116.8, 124.4, 126.2, 127.4, 127.5, 129.5, 129.6, 130.8, 135.4, 136.7, 141.2, 141.6, 153.1, 153.8; (+)-ESI-LRMS *m/z* 335 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{19}H_{20}NaO_4$ ($M+Na^+$): 335.1259. Found: 335.1263.

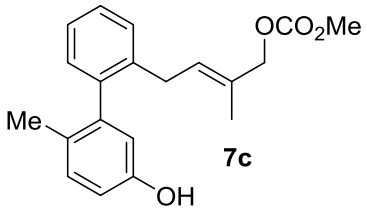
Compound 7b–7d, 7f–7i were prepared from **SI-11–SI-17** according to the general procedure described above. **Compound 7e** was prepared from **7b.**



7b

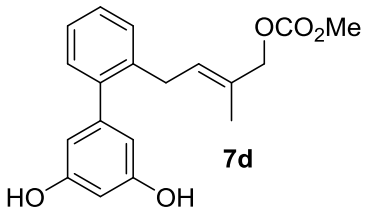
Compound 7b: White solid. IR (ATR) ν 3377, 1718, 1596, 1442, 1272, 1151, 998, 933, 752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.30 (d, *J* = 5.6 Hz, 2H), 3.78 (s, 3H), 4.60 (dd, *J* = 0.8 Hz, 6.0 Hz, 2H), 5.31–5.38 (m, 1H), 5.52 (br-s,

2H), 5.98 (dt, *J* = 15.6 Hz, 5.6 Hz, 1H), 6.35–6.39 (m, 3H), 7.21–7.33 (m, 4H); ^{13}C NMR (CD_3OD): δ 36.9, 55.2, 69.3, 102.2, 108.9 (2C), 125.8, 127.1, 128.4, 130.7 (2C), 130.7, 136.7, 137.8, 143.6, 145.0, 157.2, 159.2; (+)-ESI-LRMS *m/z* 337 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{18}H_{18}NaO_5$ ($M+Na^+$): 337.1052. Found: 337.1008.



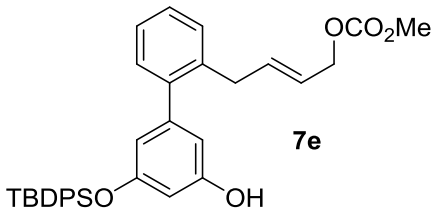
7c

Compound 7c: Colorless oil; IR (ATR) ν 3419, 2955, 1720, 1442, 1264, 938, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H), 1.94 (s, 3H), 3.11 (d, *J* = 7.0 Hz, 1H), 3.12 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 5.46 (t, *J* = 7.0 Hz, 1H), 5.63 (br-s, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 6.75 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 7.06–7.10 (m, 2H), 7.21–7.31 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 13.5, 19.0, 32.1, 54.9, 73.5, 114.3, 116.9, 126.0, 127.5, 127.7, 129.0, 129.2, 129.5, 129.6, 130.8, 137.9, 141.2, 141.7, 153.3, 155.8; (–)-ESI-LRMS *m/z* 325 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{20}H_{21}O_4$ ($[M–H]^-$): 325.1440. Found: 325.1484.



7d

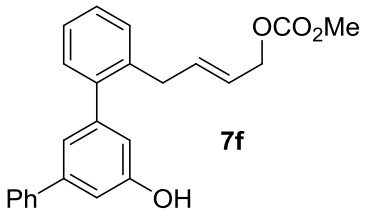
Compound 7d: White solid; IR (ATR) ν 3383, 1718, 1595, 1442, 1281, 1153, 999, 846, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 3H), 3.27 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 4.52 (s, 2H), 5.34 (br-s, 2H), 5.59 (t, *J* = 6.0 Hz, 1H), 6.33–6.36 (m, 3H), 7.20–7.32 (m, 4H); ^{13}C NMR (CD_3OD): δ 13.8, 32.7, 55.2, 74.4, 102.1, 109.0 (2C), 126.9, 128.4, 130.2 (2C), 130.2, 130.6, 131.3, 139.0, 143.6, 145.1, 157.3, 159.3; (–)-ESI-LRMS *m/z* 327 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{19}H_{19}O_5$ ($[M–H]^-$): 327.1233. Found: 327.1232.



7e

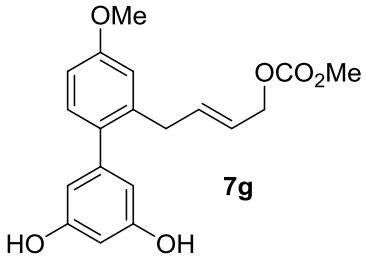
Compound 7e: To a stirred solution of phenol derivative **7b** (737 mg, 2.34 mmol) and imidazole (319 mg, 4.69 mmol) in DMF (2.3 mL) at 0 °C was added TBDPSCl (0.9 mL, 3.52 mmol), and the resulting mixture was stirred for 1 h at room temperature. After dilution with Et_2O, the mixture was washed with water (2 times), brine, and then dried over Na_2SO_4. After concentration *in vacuo*, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **7e** (351 mg, 27% yield) as a colorless oil; IR (ATR) ν 3416, 2956, 1722, 1589, 1427, 1265, 1153, 1112, 1020, 906, 730, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H), 3.08 (d, *J* =

6.0 Hz, 2H), 3.76 (s, 3H), 4.60 (d, *J* = 6.0 Hz, 2H), 5.25–5.31 (m, 1H), 5.43 (br-s, 1H), 5.76 (dt, *J* = 15.2 Hz, 6.0 Hz, 1H), 6.22 (dd, *J* = 1.4 Hz, 2.2 Hz, 1H), 6.99 (dd, *J* = 1.4 Hz, 7.8 Hz, 1H), 7.12–7.24 (m, 3H), 7.33–7.43 (m, 6H), 7.70–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 19.4, 26.4, 35.8, 54.9, 68.6, 105.9, 109.7 , 113.3, 124.5, 126.2, 127.3, 127.8 (4C), 129.8 (2C), 129.8 (2C), 129.9, 132.7, 135.5 (4C), 136.2, 136.3, 141.6, 142.9, 155.9, 156.0, 156.4; (+)-ESI-LRMS *m/z* 575 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{34}H_{36}NaO_5Si$ ($M+Na^+$): 575.2230. Found: 575.2220.



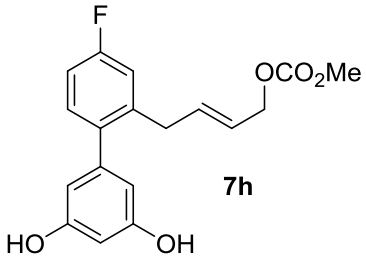
7f

Compound 7f: Colorless oil; IR (ATR) ν 3404, 1719, 1592, 1442, 1262, 1186, 906, 759, 728, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 (dd, *J* = 1.0 Hz, 6.0 Hz, 2H), 3.77 (s, 3H), 4.58 (dd, *J* = 1.0 Hz, 6.0 Hz, 2H), 5.40 (dt, *J* = 6.4 Hz, 15.6 Hz, 1H), 5.92–5.99 (m, 2H), 6.82 (t, *J* = 1.6 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 2H), 7.24–7.36 (m, 5H), 7.39–7.43 (m, 2H), 7.58–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 36.1, 54.9, 68.6, 112.8, 115.2, 120.3, 124.7, 126.4, 127.1 (2C), 127.5, 127.6, 128.7 (2C), 130.0, 130.1, 136.3, 136.4, 140.6, 141.8, 142.7, 143.1, 155.7, 156.0; (+)-ESI-LRMS *m/z* 397 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{22}NaO_4$ ($M+Na^+$): 397.1416. Found: 397.1378.



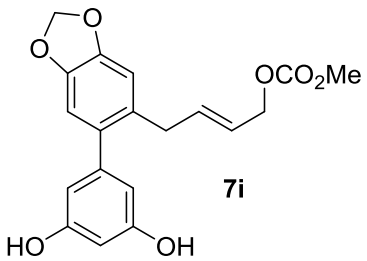
7g

Compound 7g: Colorless oil; IR (ATR) ν 3417, 2955, 1745, 1721, 1607, 1488, 1442, 1259, 1157, 1045, 973, 935, 814, 792 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H), 3.04 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H), 3.14 (dd, *J* = 5.8 Hz, 15.2 Hz, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.52 (d, *J* = 6.4 Hz, 2H), 5.26–5.37 (m, 1H), 5.66 (br-s, 1H), 5.73–5.83 (m, 1H), 6.54–6.58 (m, 1H), 6.75 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 6.77–6.83 (m, 2H), 7.00–7.05 (m, 1H), 7.06–7.11 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 19.0, 36.3, 54.8, 55.2, 68.4, 111.4, 114.2, 115.0, 117.3, 124.5, 128.0, 130.6, 130.8, 133.7, 135.2, 138.2, 141.4, 153.1, 155.8, 158.7; (–)-ESI-LRMS *m/z* 341 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{20}H_{21}O_5$ ($[M–H]^-$): 341.1389. Found: 341.1433.



7h

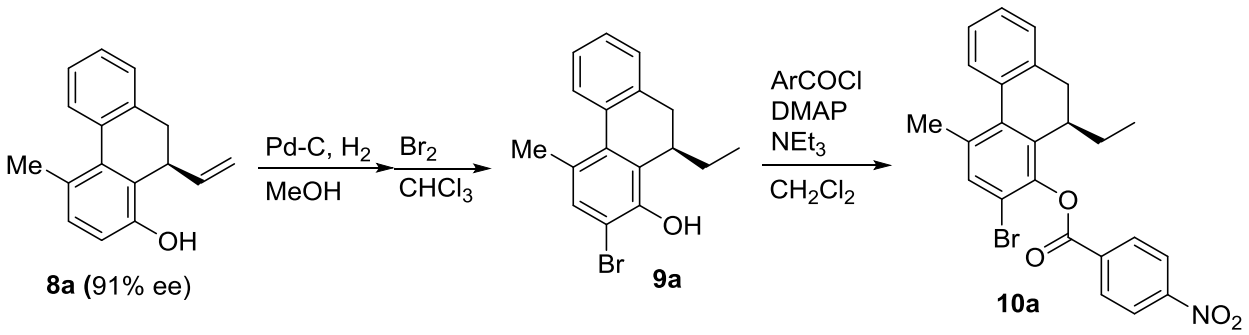
Compound 7h: Yellow oil; IR (ATR) ν 3424, 2956, 1721, 1487, 1442, 1260, 1225, 937, 868, 821, 792 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.93 (s, 3H), 3.05 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 3.15 (dd, *J* = 5.2 Hz, 15.6 Hz, 1H), 3.78 (s, 3H), 4.54 (d, *J* = 6.4 Hz, 2H), 5.27–5.37 (m, 1H), 5.45 (br-s, 1H), 5.72–5.81 (m, 1H), 6.53–6.66 (m, 1H), 6.77 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H), 6.93–6.99 (m, 2H), 7.03–7.13 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 19.0, 36.0, 54.9, 68.2, 113.1 (d, *J* = 21.0 Hz), 114.6, 116.1 (d, *J* = 21.0 Hz), 117.0, 125.1, 127.8, 130.9, 131.1 (d, *J* = 7.6 Hz), 134.5, 137.0 (d, *J* = 3.8 Hz), 139.2 (d, *J* = 6.7 Hz), 140.6, 153.2, 155.8, 162.0 (d, *J* = 245.1 Hz); (–)-ESI-LRMS *m/z* 329 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{19}H_{18}FO_4$ ($[M–H]^-$): 329.1189. Found: 329.1215.



7i

Compound 14i: Colorless oil, IR (ATR) ν 3420, 2957, 1732, 1480, 1263, 1038, 906, 726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.96 (s, 3H), 2.95 (dd, *J* = 1.2 Hz, 15.6 Hz, 1H), 3.06 (dd, *J* = 2.0 Hz, 15.6 Hz, 1H), 3.78 (s, 3H), 4.54 (d, *J* = 6.4 Hz, 1H), 5.27–5.34 (m, 1H), 5.52 (br-s, 1H), 5.75 (dt, *J* = 6.4 Hz, 15.2 Hz, 1H), 5.96 (s, 1H), 5.97 (s, 1H), 6.55 (d, *J* = 6.4 Hz, 1H), 6.58 (s, 1H), 6.72 (s, 1H), 6.75 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.0, 35.8, 54.9, 68.4, 101.0, 109.5, 109.7, 114.4, 117.1, 124.3, 127.9, 130.1, 130.9, 134.3, 135.6, 141.4, 145.8, 146.8, 153.1, 155.8; (+)-ESI-LRMS *m/z* 379 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{20}H_{20}NaO_6$ ($M+Na^+$): 379.1158. Found: 379.1119.

1-4. Determination of the Absolute Configuration of 10a



Compound 9a: A suspension of **8a** (188 mg, 0.80 mmol) and Pd-C (5%, 35 mg) in MeOH (5 mL) was stirred for 4 h under H_2 atmosphere. The mixture was filtered through a short pad of celite, and the obtained solution was evaporated *in vacuo*. The obtained residue was utilized for the next reaction. To a stirred solution of the obtained product in $CHCl_3$ (8 mL) was added Br_2 (49 μL, 0.96 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of aq. $Na_2S_2O_3$ solution, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration *in vacuo*, the obtained crude residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 40/1) to give **9a** [218.4 mg, 86% yield (2 steps)] as white amorphous solids. IR (ATR) ν 2927, 1746, 1527, 1346, 1256, 1216, 1080, 1061, 847, 750, 715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83–1.36 (m, 5H), 2.53 (s, 3H), 2.79 (dd, *J* = 2.0 Hz, 14.8 Hz, 1H), 2.87 (dd, *J* = 4.8 Hz, 14.8 Hz, 1H), 3.27–3.32 (m, 1H), 5.39 (s, 1H), 7.20–7.28 (m, 4H), 7.60 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 12.1, 22.3, 23.3, 33.0, 34.2, 108.8, 125.8, 127.2, 127.8, 128.1, 128.8, 130.8, 132.2, 133.8, 134.4, 137.1, 146.9; (–)-ESI-LRMS *m/z* 315 ($[M–H]^-$); (–)-ESI-HRMS. Calcd for $C_{17}H_{16}BrO$ ($[M–H]^-$): 315.0385. Found: 315.0382; $[\alpha]_D^{18}$ +122.8 [*c* 0.73, $CHCl_3$, 91% ee (*R*)].

Compound 10a: To a stirred solution of **9a** (110 mg, 0.347 mmol), DMAP (8.5 mg, 0.0694 mmol), and NEt_3 (0.14 mL, 1.04 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C was added *p*-nitrobenzoyl chloride (129 mg, 0.694 mmol), and the reaction was kept stirring for 3 h at room temperature. The reaction was quenched by the addition of water and the resulting mixture was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The obtained crude residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 50/1) to give **10a** (161 mg, 99% yield) as white solids. Single recrystallization of the product from hexane-ethyl acetate gave compound **10a** with 99% ee (colorless needle). Mp. 148–149 °C; IR (ATR) ν 2960, 1745, 1526, 1346, 1256, 1216, 1079, 1061, 847, 732, 715 cm^{-1}; ^1H NMR ($CDCl_3$, mixture of rotational isomers): δ 0.60–0.85 (m, 3H), 1.13–1.28 (m, 2H), 2.62 (s, 3H), 2.70–3.08 (m, 3H), 7.24–7.33 (m, 3H), 7.50 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 8.39–8.46 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 12.3, 22.7, 24.0, 33.3, 36.0, 114.2, 123.9 (2C), 123.9, 126.1, 127.6, 127.9, 128.9, 131.5 (2C), 133.1, 134.1, 134.3, 134.6, 134.8, 136.7, 137.0, 151.1, 162.5; EI-LRMS *m/z* 465 (M^+) 467 (M^++2); EI-HRMS. Calcd for $C_{24}H_{20}BrNO_4$ (M^+): 465.0576. Found: 465.0536; $[\alpha]_D^{17}$ +36.5 [*c* 0.40, $CHCl_3$, 99% ee (*R*)]. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow rate: 0.5 mL/min, t_R 11.6 min [(*R*)-isomer] and 16.0 min [(*S*)-isomer], detection at 254 nm).

X-ray Analysis:

A single crystal (ca. 0.30 x 0.30 x 0.12 mm) suitable for X-ray analysis was obtained from hexane-AcOEt solution. The representative data are summarized in Table S-1.

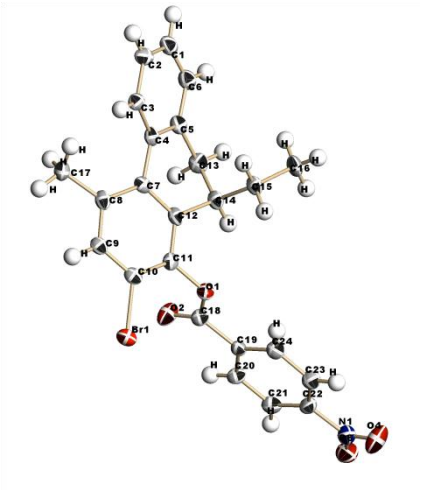


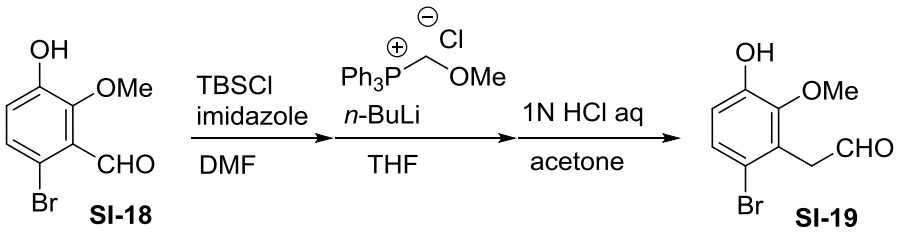
Table S-1.

Identification code	nemo017p2(1)2(1)2(1)
Empirical formula	C24 H20 Br N O4
Formula weight	466.32
Temperature	173 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 7.7671(9) Å (α = 90°).
	b = 13.4242(16) Å (β = 90°)
	c = 19.659(2) Å (γ = 90 °)
Volume	2049.8(4) $Å^3$
Z	4
Density (calculated)	1.511 Mg/m^3
Absorption coefficient	2.037 mm^{-1}
F(000)	952
Crystal size	0.3 x 0.3 x 0.12 mm^3
Theta range for data collection	1.84 to 28.61°.
Index ranges	-10<=h<=9, -15<=k<=17, -24<=l<=26
Reflections collected	11754
Independent reflections	4706 [R(int) = 0.0325]
Completeness to theta = 28.61°	92.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	4706 / 0 / 271
Goodness-of-fit on F^2	0.756
Final R indices [I>2sigma(I)]	R1 = 0.0466, wR2 = 0.1363
R indices (all data)	R1 = 0.0668, wR2 = 0.1621
Absolute structure parameter	–0.019 (17)
Largest diff. peak and hole	65.686 and -15.732 e.$Å^{-3}$

1-5. Enantioselective Total Synthesis of Cedrelin A and Paralycolin B.

1-5-1. Experimental Procedure for the Preparation of 11a and 11b

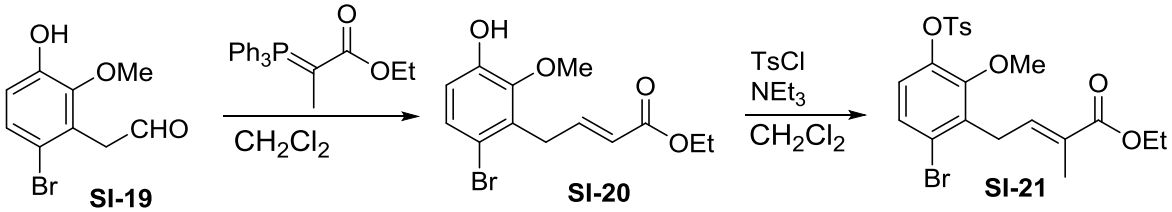


Compound SI-19: To a stirred solution of **SI-18** (7.44 g, 32.2 mmol) and imidazole (2.85 g, 41.9 mmol) in DMF (32.2 mL) at 0 °C was added TBSCl (7.28 g, 48.3 mmol), and the resulting mixture was stirred for 1 h at room temperature. After dilution with Et_2O, the mixture was washed with water (2 times), brine, and then dried over Na_2SO_4. After concentration in *vacuo*, the obtained crude silylated product was used for the next step without purification.

To a stirred solution of (methoxymethyl)triphenyl phosphonium chloride (16.8 g, 48.9 mmol) in THF (120 mL) at 0 °C was added KO*t*-Bu (12.8 g, 114.0 mmol). The resulting mixture was stirred at the same temperature for 30 min. A solution of the crude silylated product in THF (40 mL) was added to the reaction, and then the resulting mixture was stirred at room temperature. After 2 h, the reaction was quenched with 1 N aq HCl, and the mixture was diluted with AcOEt. After separation of the aqueous layer, the organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in *vacuo*. The obtained crude methyl vinyl ether derivative was used for the next step without purification.

To a stirred solution of the crude product in THF (72 mL) at room temperature was added 1 N aq HCl (10 mL). The resulting solution was refluxed for 3 h. After evaporation of the organic solvent in vacuo, water was added to the mixture, and the resulting slurry was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **SI-18** (7.10 g, 90% yield over three steps) as white solid. Mp 74–75 °C; IR (ATR) ν 3379, 2943, 2836, 1713, 1466, 1427, 1287, 1179, 1030, 998, 807 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.71 (s, 3H), 3.91 (d, J = 1.2 Hz, 2H), 6.24 (br-s, 1H), 6.80 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 9.75 (t, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 44.8, 61.3, 114.8, 116.8, 126.9, 128.6, 146.8, 148.5, 199.0; (+)-ESI-LRMS m/z 267 ($M+Na^+$), 269 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_9H_9BrNaO_3^+$ ($M+Na^+$): 266.9627. Found: 266.9628.

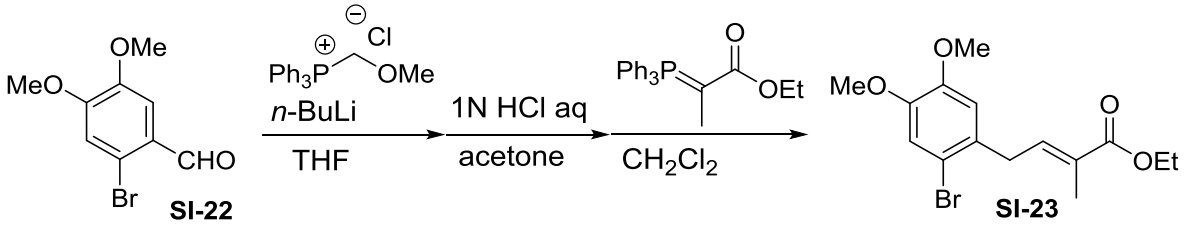
Compound SI-18: Commercially Available.



Compound SI-20: To a stirred solution of aldehyde **SI-19** (980 mg, 4.00 mmol) in CH_2Cl_2 (20 mL) at room temperature was added a Wittig reagent (1.66 g, 13.5 mmol), and the resulting mixture was stirred for 1 h at the

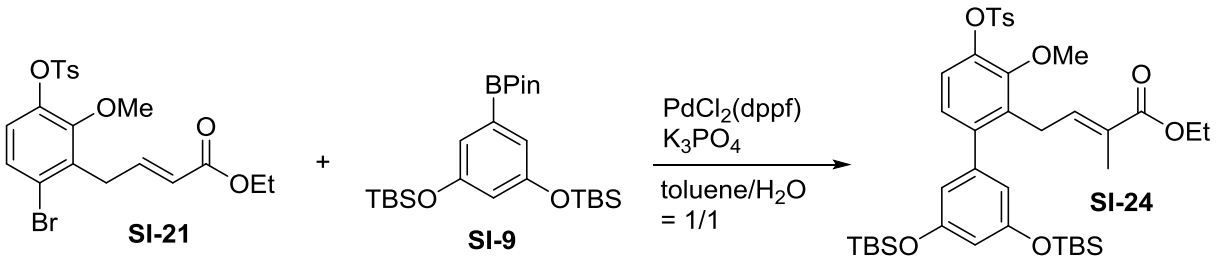
same temperature. After evaporation of the solvent, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1) to give **SI-20** (1.09 g, 83% yield) as colorless oil. IR (ATR) ν 3370, 2981, 1685, 1467, 1293, 1257, 1176, 1001, 907, 808, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.02 (d, *J* = 1.6 Hz, 3H), 3.66 (d, *J* = 7.0 Hz, 2H), 3.77 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.69 (br-s, 1H), 6.71 (td, *J* = 1.6 Hz, 7.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.1, 29.9, 60.7, 61.2, 114.3, 115.8, 128.2, 128.5, 132.4, 139.2, 146.4, 148.7, 168.4; (+)-ESI-LRMS m/z 351 ($M+Na^+$), 353 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{14}H_{17}BrNaO_4^+$ ($M+Na^+$): 351.0202. Found: 351.0184.

Compound SI-21: To a stirred solution of 5 (1.09 g, 3.30 mmol) and triethylamine (0.55 mL, 3.96 mmol) in CH_2Cl_2 (6.6 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1.66 g, 13.5 mmol), and the resulting mixture was stirred at room temperature. After 1 h, the reaction was quenched with water, and the mixture was diluted with AcOEt. After separation of the aqueous layer, the organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1) to give **SI-21** (1.42 g, 90% yield) as white solid. Mp 70–71 °C; IR (ATR) ν 2980, 1707, 1466, 1378, 1254, 1178, 1007, 818 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.94 (d, *J* = 1.2 Hz, 3H), 2.46 (s, 3H), 3.59 (d, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 6.55 (td, *J* = 1.2 Hz, 6.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.3, 21.7, 30.2, 60.6, 61.5, 123.1, 123.3, 128.0, 128.4 (2C), 128.7, 129.7 (2C), 132.5, 134.4,137.7,145.7,151.7,167.9; (+)-ESI-LRMS m/z 505 ($M+Na^+$), 507 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{21}H_{23}BrNaO_6S^+$ ($M+Na^+$): 505.0291. Found: 505.0313.

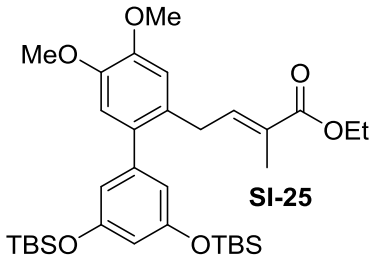


Compound SI-23 was prepared from **SI-22** according to the experimental procedure described above (82% yield, three steps). White solid. Mp 35–36 °C; IR (ATR) ν 2934, 1707, 1507, 1440, 1381, 1255, 1219, 1164, 1116, 1071, 1032, 800 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.98 (s, 3H), 3.56 (d, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 6.69 (s, 1H), 6.79 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 12.7, 14.2, 35.0, 56.1, 56.2, 60.6, 113.0, 114.2, 115.7, 128.8, 130.5, 138.9, 148.3, 148.6, 167.9; (+)-ESI-LRMS m/z 365 ($M+Na^+$), 367 ($M+2+Na^+$); (+)-ESI-HRMS. Calcd for $C_{15}H_{19}BrNaO_4^+$ ($M+Na^+$): 365.0359. Found: 365.0365.

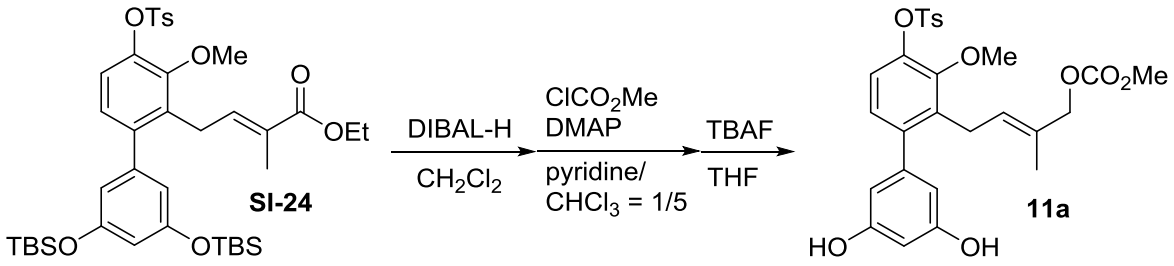
Compound SI-22: Commercially Available.



Compound SI-24: A mixture of **SI-21** (2.78 g, 5.76 mmol), **SI-9** (3.21 g, 6.91 mmol), $PdCl_2$(dppf) (170 mg, 0.29 mmol), and K_3PO_4 (3.67 g, 17.3 mmol) in toluene (5 mL) and H_2O (5 mL) was stirred for 24 h at 90 °C. After the reaction was quenched with water, AcOEt was added to the mixture. The aqueous layer was separated and the resulting organic layer was washed with brine, dried over Na_2SO_4, and then evaporated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 30/1) to give **SI-24** (4.18 g, 98% yield) as white solid. Mp 107–108 °C; IR (ATR) ν 2931, 1714, 1585, 1379, 1255, 1166, 1029, 831, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.18 (s, 12H), 0.97 (s, 18H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.67 (d, *J* =1.2 Hz, 3H), 2.47 (s, 3H), 3.38 (d, *J* = 6.8 Hz, 2H), 3.73 (s, 3H), 4.14 (q, *J* = 6.8 Hz, 2H), 6.32 (s, 2H), 6.32 (s, 1H), 6.53 (dt, *J* = 1.2 Hz, 6.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ –4.5 (4C), 12.3, 14.3, 18.1 (2C), 21.7, 25.6 (6C), 27.6, 60.3, 61.1, 111.1, 114.4 (2C), 121.7, 125.1, 127.5, 128.4 (2C), 129.7 (2C), 132.3, 133.1, 140.2, 141.7, 141.9, 142.2, 145.4, 150.8, 156.3 (2C), 167.8; (+)-ESI-LRMS m/z 763 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{39}H_{56}NaO_8SSi_2^+$ ($M+Na^+$): 763.3127. Found: 763.3166.



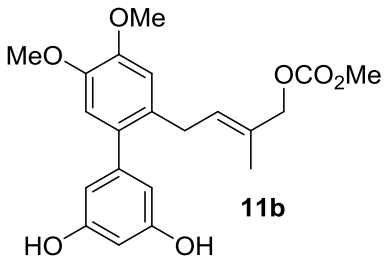
Compound SI-25 was prepared from **SI-23** and **SI-9** according to the experimental procedure described above (92% yield). White solid. Mp 70–71 °C; IR (ATR) ν 2930, 1711, 1584, 1516, 1432, 1256, 1164, 1028, 832, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.20 (s, 12H), 0.98 (s, 18H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.78 (d, *J* = Hz, 3H) 3.42 (d, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 6.33 (t, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 2H), 6.72 (s, 1H), 6.74 (s, 1H), 6.79 (td, *J* = 1.2 Hz, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ –4.4 (4C), 12.4, 14.2, 18.2 (2C), 25.6 (6C), 32.3, 56.0, 56.0, 60.4, 110.7, 112.3, 113.1, 114.7 (2C), 127.7, 128.7, 134.2, 141.0, 142.9, 147.2, 148.4, 156.2 (2C), 167.9; (+)-ESI-LRMS m/z 623 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{33}H_{52}NaO_6Si_2^+$ ($M+Na^+$): 623.3195. Found: 623.3222.



Compound 11a: To a stirred solution of **SI-24** (4.08 g, 6.95 mmol) in CH2Cl2 (35 mL) at –78 °C was added DIBAL-H (17.4 mL, 1 M solution in hexane, 17.4 mmol). After the solution was stirred for 2.5 h at –78 °C, and 30 min at room temperature, the reaction was quenched by the addition of aq 1M Rochelle salt. After being stirred for 1 h, the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in *vacuo*. The obtained crude alcohol was used for the next step without purification.

To a stirred solution of crude alcohol and DMAP (170 mg, 1.39 mmol) in $CHCl_3$ (11.6 mL) and pyridine (2.3 mL) at 0 °C was added methyl chloroformate (1.34 mL, 17.4 mmol), and the resulting mixture was kept stirring for 3 h at room temperature. The reaction was quenched with 1 N HCl at 0 °C, and then the resulting mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in *vacuo*. The obtained residue was used for the next reaction without further purification.

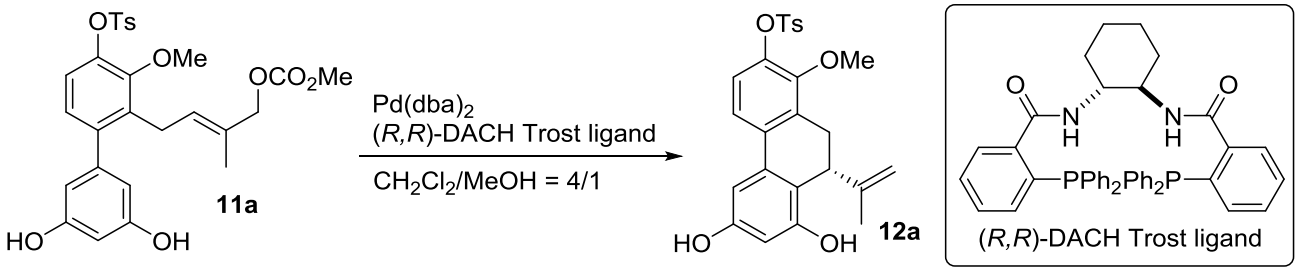
To a stirred solution of the crude sample in THF (35 mL) at 0 °C was added TBAF (17.4 mL, 1 M solution in THF, 0.73 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with AcOEt. The obtained mixture was washed with water and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 2/1) to give **11a** (3.10 g, 85% yield over three steps) as amorphous solid. IR (ATR) ν 3420, 2955, 1721, 1598, 1472, 1442, 1370, 1254, 1189, 1174, 1154, 983, 749, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (s, 3H), 2.46 (s, 3H), 3.18 (d, J¼5.6 Hz, 2H), 3.73 (s, 3H) 3.78 (s, 3H), 4.47 (s, 2H), 5.32 (t, J¼5.6 Hz, 1H), 6.16e6.25 (m, 4H), 6.36 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.7, 21.7, 26.7, 55.1, 61.2, 73.6, 101.7, 108.8 (2C), 121.3, 125.1, 128.4 (2C), 129.2, 129.6, 129.7, 129.7 (2C), 132.9, 133.4, 141.6, 142.2, 145.4, 150.6, 156.2, 156.7 (2C); (+)-ESI-LRMS m/z 551 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{27}H_{28}NaO_9S^+$ ($M+Na^+$): 551.1346. Found: 551.1369.



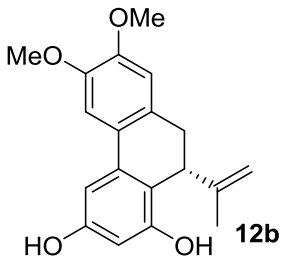
Compound 11b was prepared from **SI-25** according to the experimental procedure described above (94% yield). Amorphous solid; IR (ATR) ν 3418, 2959, 1724, 1600, 1507, 1442, 1255, 1156, 1059, 1000, 776 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.56 (s, 3H), 3.22 (d, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.53 (s, 2H), 5.59 (t, *J* =

6.4 Hz, 2H), 6.00 (br-s, 2H), 6.33 (d, J = 2.0 Hz, 2H), 6.36 (t, J = 2.0 Hz, 1H), 6.72 (s, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 32.0, 55.0, 55.9, 55.9, 73.7, 101.2, 109.1 (2C), 112.6, 112.8, 129.1, 130.0, 130.6, 133.9, 143.5, 146.9, 148.1, 156.1, 156.6 (2C); (+)-ESI-LRMS m/z 411 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{21}H_{24}NaO_7^+$ ($M+Na^+$): 411.1414. Found: 411.1430.

1-5-2. Experimental Procedure for the Pd-catalyzed Intramolecular Friedel–Crafts Allylic Alkylation of Phenols.



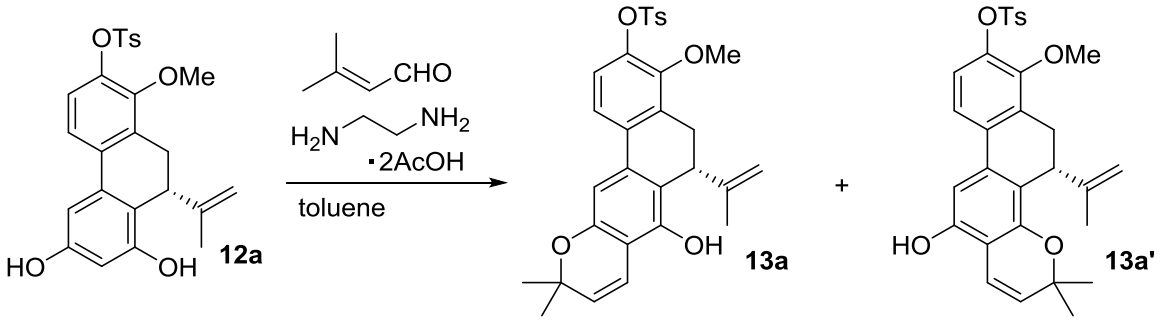
Compound 12a: Compound **11a** (123 mg, 0.233 mmol), $Pd(dba)_2$ (13.4 mg, 0.0233 mmol), (*R,R*)-DACH Trost ligand (19.3 mg, 0.0279 mmol), and KOAc (34.2 mg, 0.349 mmol) were dissolved in THF (3.7 mL) and MeOH (0.93 mL) under argon atmosphere, and the resulting solution was stirred at 40 °C. After 12 h, the reaction was quenched with water, and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH = 30/1) to give **12a** (99.0 mg, 94% yield) as amorphous solid. IR (ATR) ν 3461, 1616, 1465, 1362, 1254, 1174, 1011, 967, 830, 754, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.44 (s, 3H), 2.56–2.62 (m, 1H), 3.28 (d, J = 16.0 Hz, 1H), 3.69 (s, 3H), 3.73 (d, J = 6.0 Hz, 1H), 4.29 (s, 1H), 4.59 (s, 1H), 5.53 (br-s, 1H), 5.80 (br-s, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.0, 21.7, 25.6, 37.1, 61.2,103.1,103.8,112.2,117.0,119.8,121.3,128.4 (2C),129.6 (2C), 130.2, 132.6, 134.4, 135.5, 141.8, 145.2, 145.3, 149.6, 154.1, 155.4; (+)-ESI-LRMS m/z 475 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{25}H_{24}NaO_6S^+$ ($M+Na^+$): 475.1186. Found: 475.1199; $[\alpha]_D^{14}$ –71.8 (c 1.27, $CHCl_3$, 66% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 80/20, flow rate: 1.0 mL/min, tR 9.3 min [(*R*)-(–)-isomer] and 13.1 min [(*S*)-(+)-isomer], detection at 254 nm).



Compound 12b was prepared from **11b** according to the experimental procedure described above (98% yield, 92% ee). White solid. Mp 139–140 °C; IR (ATR) ν 3409, 2938, 1606, 1578, 1515, 1464, 1257, 1205,1139,1012, 756 cm–1; 1H NMR ($CDCl_3$): δ 1.67 (s, 3H), 2.93 (dd, J = 2.8 Hz, 15.2 Hz, 1H), 3.09 (dd, J = 7.2 Hz, 15.2 Hz, 1H),

3.72 (dd, *J* =2.8 Hz, 7.2 Hz, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.53 (s, 1H), 4.72 (s, 1H), 4.78 (s, 1H), 4.98 (s, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 6.69 (s, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 7.15 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 33.8, 38.5, 56.4, 56.8, 102.2, 102.5, 109.2, 111.6, 113.4, 117.7, 128.8, 130.0, 137.4, 147.0, 149.0, 150.0, 156.6, 157.8 (+)-ESI-LRMS m/z 313 (M+H+); (+)-ESI-HRMS. Calcd for $C_{19}H_{21}O_4^+$ ($M+H^+$): 313.1434. Found: 313.1454; $[\alpha]_D^{26}$ –105.5 (c 0.52, MeOH, 92% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 80/20, flow rate: 1.0 mL/min, tR 13.5 min [(*S*)-(+)-isomer] and 24.0 min [(*R*)-(–)-isomer], detection at 254 nm).

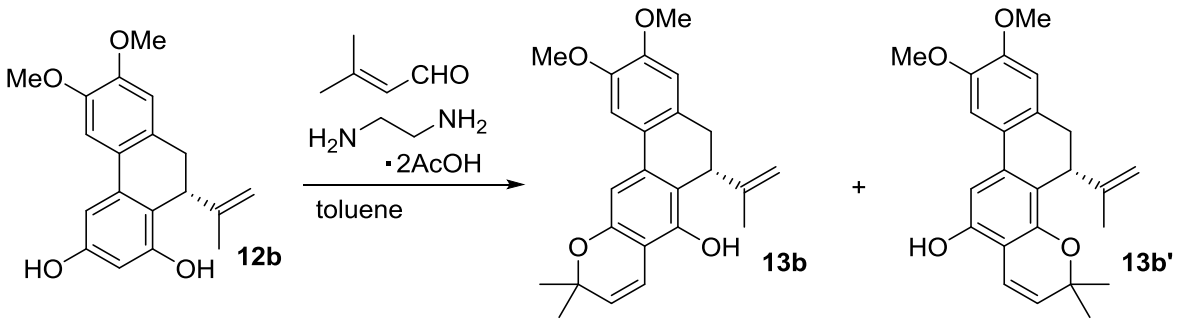
1-5-3. Experimental Procedure for the Formation of the Chromene Ring



To a stirred solution of **12a** (25.3 mg, 0.081 mmol) and ethylendiamine diacetate (0.7 mg, 0.0041 mmol) in toluene (1.60 mL), was added 3-methyl crotonaldehyde (12.4 mL, 0.121 mmol), and the resulting mixture was refluxed for 6 h. Then, the solvent was removed in vacuo, and the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1 to 3/1) to give **13a** (15.6 mg, 51% yield) and as a brown oil, and **13a'** (11.6 mg, 38% yield) as a brown oil.

Compound 13a: IR (ATR) ν 3528, 2925, 1470, 1373, 1255, 1175, 1122, 827, 771, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 3H), 1.48 (s, 3H), 1.54 (s, 3H), 2.44 (s, 3H), 2.72 (dd, *J* = 7.2 Hz, 16.0 Hz, 1H), 3.29 (dd, *J* = 2.4 Hz, 16.0 Hz, 1H), 3.64 (dd, *J* = 2.4 Hz, 7.2 Hz, 1H), 3.70 (s, 3H), 4.54 (s, 1H), 4.69 (s, 1H), 4.99 (br-s, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 10.0 Hz, 1H), 6.86 (s, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 20.4, 21.7, 25.7, 27.5, 28.0, 38.5, 61.2, 75.9, 105.1, 110.0, 112.8, 116.1, 116.4, 119.7, 121.5, 128.5 (2C), 129.4, 129.5 (2C), 129.9, 132.8, 134.2, 134.3, 141.8, 145.2, 145.9, 148.9, 149.6, 152.7; (+)-ESI-LRMS m/z 541 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{30}H_{30}NaO_6S^+$ ($M+Na^+$): 541.1655. Found: 541.1635; $[\alpha]_D^{26}$ –68.8 (c 1.93, $CHCl_3$, 66% ee).

Compound 13a': IR (ATR) ν 3464, 2973, 1474, 1409, 1371, 1255, 1190, 1175, 1120, 1060, 967, 829, 775, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 1.57 (s, 3H), 2.43 (s, 3H), 2.51 (dd, *J* = 6.4 Hz, 15.6 Hz, 1H), 3.26 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 3.80 (d, *J* = 6.4 Hz, 1H), 4.14 (s, 1H), 4.49 (s, 1H), 5.26 (br-s, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 6.62 (s, 1H), 6.66 (d, *J* = 10.0 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.7, 25.5, 27.1, 28.1, 35.9, 61.2, 75.9, 103.0, 109.5, 111.4, 116.7, 119.1, 119.3, 121.2, 128.5 (2C), 129.5, 129.5 (2C), 130.7, 132.7, 133.9, 134.5, 141.7, 145.1, 145.2, 149.7, 150.2, 150.8; (+)-ESI-LRMS m/z 541 ($M+Na^+$); (+)-ESI-HRMS. Calcd for $C_{30}H_{30}NaO_6S^+$ ($M+Na^+$): 541.1655. Found: 541.1635; $[\alpha]_D^{26}$ –62.3 (c 1.64, $CHCl_3$, 66% ee).

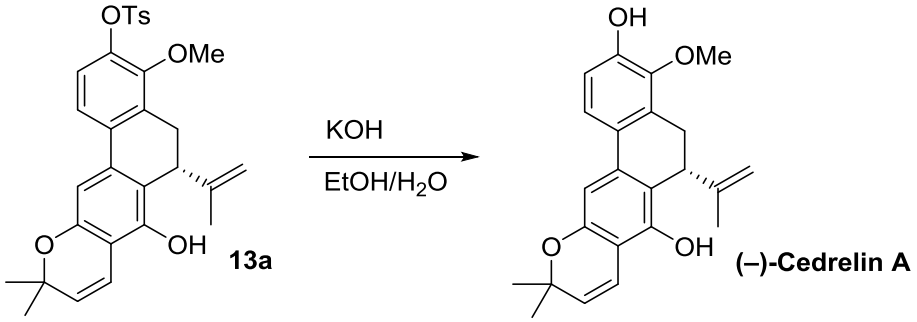


Compound 13b was prepared from **12b** according to the experimental procedure described above (**13b**: 55% yield. **13b'**: 28% yield).

Compound 13b: Pale brown amorphous solid; IR (ATR) ν 3431, 2970, 2926, 1606, 1552, 1515, 1433, 1258, 1216, 1126 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 3H), 1.50 (s, 3H), 1.63 (s, 3H), 2.91 (dd, *J* = 2.4 Hz, 15.6 Hz, 1H), 3.11 (dd, *J* = 7.0 Hz, 15.6 Hz, 1H), 3.65 (dd, *J* = 2.4 Hz, 7.0 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.67 (s, 1H), 4.75 (s, 1H), 5.06 (br-s, 1H), 5.61 (d, *J* = 9.6 Hz, 1H), 6.66 (s, 1H), 6.67 (d, *J* = 9.6 Hz, 1H), 6.86 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3, 27.6, 28.1, 33.1, 39.4, 55.9, 55.9, 75.9, 104.0, 107.1, 108.9, 111.1, 112.6, 115.3, 116.6, 126.3, 127.0, 128.9, 135.3, 146.9, 147.8, 148.7, 149.2, 152.6; (+)-ESI-LRMS m/z 379 (M+H+); (+)-ESI-HRMS. Calcd for $C_{24}H_{27}O_4^+$ ($M+H^+$): 379.1904. Found: 379.1918; $[a]_D^{23}$ –94.0 (c 0.44, CHCl3, 92% ee).

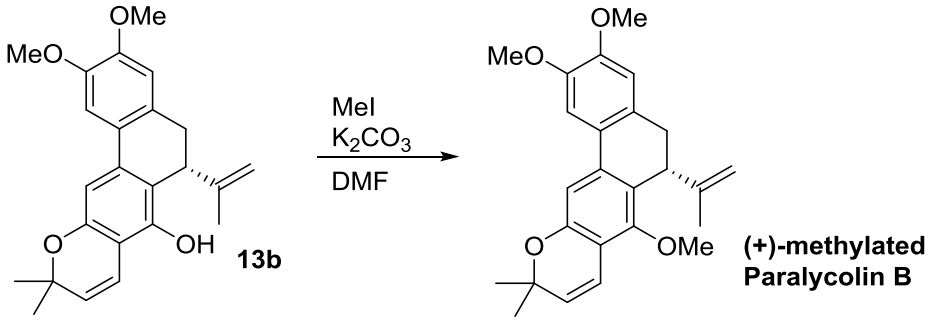
Compound 13b': White solid Mp 160–161 °C; IR (ATR) ν 3441, 2962, 1514, 1431, 1264, 1206, 1114, 1067, 1036 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.47 (s, 3H), 1.68 (s, 3H), 2.89 (dd, *J* = 0 Hz, 15.6 Hz, 1H) 3.03 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 3.84 (dd, *J* = 2.0 Hz, 6.8 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 4.30 (s, 1H), 4.58 (s, 1H), 4.78 (br-s, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 10.0 Hz, 1H), 6.68 (s, 1H), 6.70 (s, 1H), 7.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 27.1, 28.2, 32.7, 36.8, 55.8, 56.0, 75.8, 102.1, 106.8, 108.4, 111.3, 111.7, 116.6, 118.7, 126.3, 128.5, 129.0, 135.1, 146.0, 147.6, 148.7, 150.0, 151.0; (+)-ESI-LRMS m/z 379 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{24}H_{27}O_4^+$ ($M+H^+$): 379.1904. Found: 379.1919; $[\alpha]_D^{26}$ –27.2 (c 1.18, $CHCl_3$, 92% ee).

1-5-4. Synthesis of Cedrelin A and Methylated Pralycolin B

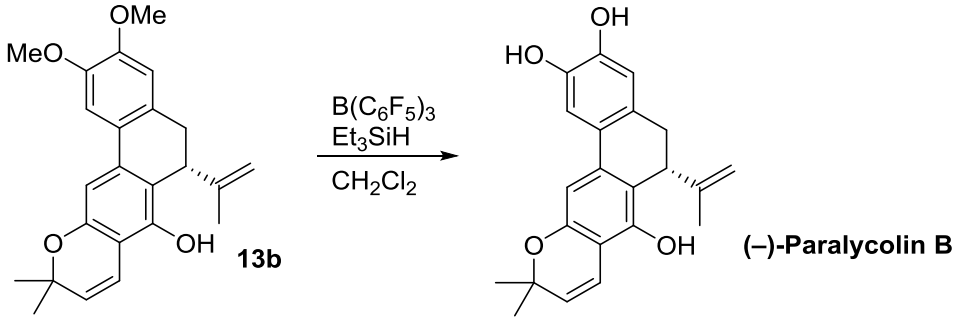


(–)-Cedrelin A: Solution of potassium hydroxide (3.0 g) in water (50 mL) and ethanol (50 mL) was prepared. **13a** (38.6 mg, 0.074 mmol) was dissolved in 2.0 mL of the alkaline solution, and the resulting mixture was stirred at 80 °C. After 1 h, the solution was cooled, and neutralized with acetic acid. The mixture was extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 7/1) to give **cedrelin A** (20.0 mg, 74% yield) as pale yellow oil; IR (ATR) ν 3441, 2973, 1604, 1558, 1474, 1291, 1167, 1121, 1027, 899, 753 cm^{-1}; ^1H NMR

($CDCl_3$): d 1.43 (s, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 2.89 (dd, *J* = 7.2 Hz, 15.6 Hz, 1H), 3.32 (dd, *J* = 2.8 Hz,15.6 Hz, 1H), 3.96–3.71 (m, 1H), 3.78 (s, 3H), 4.64 (s, 1H), 4.73 (s, 1H), 4.98 (s, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 5.64 (s, 1H), 6.65 (d, *J* = 10.0 Hz, 1H), 6.86 (s, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.4, 26.4, 27.5, 28.0, 38.7, 61.2, 75.8, 104.3, 109.0, 112.8, 113.6, 115.1, 116.5, 120.9, 127.6, 127.7, 129.2, 135.2, 144.3, 146.4, 148.4, 148.9, 152.7; (+)-ESI-LRMS m/z 365 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{23}H_{25}O_4^+$ ($M+H^+$): 365.1747. Found: 365.1761; $[\alpha]_D^{24}$ –54.9 (c 0.75, $CHCl_3$, 66% ee). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane/2-propanol = 90/10, flow rate: 0.75 mL/min, tR 14.7 min [(*S*)-(+)-isomer] and 17.4 min [(*R*)-(–)-isomer], detection at 254 nm).



(+)-methylated Paralycolon B: To a stirred mixture of **13b** (10.0 mg, 0.0264 mmol) and K_2CO_3 (11.0 mg, 0.0793 mmol) in DMF (0.5 mL) at 0 °C was added iodomethane (5.0 mL), and the resulting mixture was kept stirring for 5 h. After dilution of the reaction mixture with Et_2O, the mixture was washed with water and brine, and then dried over Na_2SO_4. After concentration under reduced pressure, the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 6/1) to give **methylated Paralycolon B** (9.5 mg, 92% yield) as white solid. Mp 157–158 °C IR (ATR) ν 2958, 1604, 1550, 1514, 1469, 1455, 1261, 1224, 1080, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 3H), 1.50 (s, 3H), 1.74 (s, 3H), 2.89 (dd, *J* = 2.0 Hz, 15.6 Hz, 1H), 3.03 (d, *J* = 6.4 Hz, 15.6 Hz, 1H), 3.76 (s, 3H), 3.81 (dd, *J* = 2.0 Hz, 6.4 Hz, 1H), 3.89 (s, 3H), 3.92 (s, 3H), 4.26 (s, 1H), 4.64 (s, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 6.60 (d, *J* = 10.0 Hz, 1H), 6.66 (s, 1H), 6.98 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.7, 27.7, 28.0, 32.8, 37.9, 55.8, 55.9, 62.3, 75.9, 106.8, 107.0, 111.5, 112.9, 113.4, 117.4, 123.5, 126.5, 127.7, 129.8, 135.8, 146.1, 147.7, 148.6, 152.6, 153.6; (+)-ESI-LRMS m/z 393 ($M+H^+$); (+)-ESI-HRMS. Calcd for $C_{25}H_{29}O_4^+$ ($M+H^+$): 393.2060. Found: 393.2075; $[\alpha]_D^{26}$ +15.5 (c 0.36, $CHCl_3$, 92% ee).



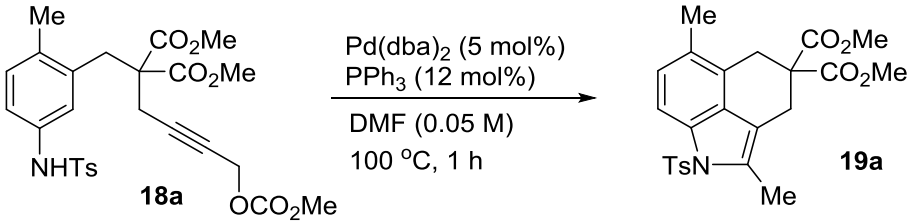
(+)-methylated Paralycolon B: 13b (82 mg, 0.217 mmol), $B(C_6F_5)_3$ (5.5 mg, 0.018 mmol) and triethylsilane (76 μL, 0.477 mmol) were dissolved in CH_2Cl_2 (2.2 mL) under argon atmosphere, and the resulting solution was stirred

at room temperature. After 12 h, the reaction was added TBAF (0.18 mL, 0.184 mmol) and the mixture was stirred for another 30 min at same temperature. Then, the reaction quenched with water, extracted with AcOEt, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, $CHCl_3$/MaOH = 30/1) to give **Paralycolon B** (39.5 mg, 52% yield) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.49 (s, 3H), 1.61 (s, 3H), 2.85 (dd, *J* = 2.0 Hz, 15.2 Hz, 1H), 3.03 (d, *J* = 6.8 Hz, 15.2 Hz, 1H), 3.62 (dd, *J* = 2.0 Hz, 6.8 Hz, 1H), 4.62 (s, 1H), 4.72 (s, 1H), 5.41 (br-s, 3H), 5.61 (d, *J* = 10.0 Hz, 1H), 6.66 (d, *J* = 10.0 Hz, 1H), 6.67 (s, 1H), 6.76 (s, 1H), 7.12 (s, 1H)

2. Synthesis of 3,4-Fused Indoles

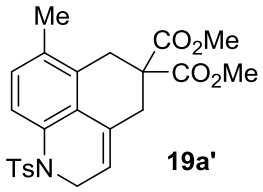
2-1. General Procedure for the Pd-Catalyzed Cascade Cyclization and Characterization of the Reaction Products

2-1-1. General Procedure for the Pd-Catalyzed Cascade Cyclization

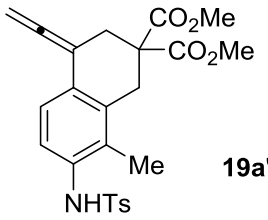


General Procedure: 18a (51.2 mg, 0.0963 mmol), $Pd(dba)_2$ (2.8 mg, 0.00482 mmol), and PPh_3 (3.0 mg, 0.0116 mmol) were dissolved in DMF (1.9 mL), and the resulting solution was stirred at 100 °C. After 1 h, the reaction was quenched with water, and the mixture was extracted with AcOEt/Hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1) to give **19a** (16.1 mg, 37% yield) as white solid.; Mp 121–122 °C; IR (ATR) ν 1733, 1436, 1353, 1240, 1174, 1158, 1089, 1060, 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.33 (s, 3H), 2.48 (s, 3H), 3.18 (s, 2H), 3.33 (s, 2H), 3.61 (s, 6H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 12.8, 17.5, 21.5, 27.7, 31.4, 52.9 (2C), 55.6, 112.4, 114.7, 125.1, 126.2 (2C), 126.6, 127.3, 129.3, 129.7 (2C), 130.5, 133.3, 136.4, 144.3, 171.1 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_6S^+$ ($M+Na^+$): 478.1295. Found: 478.1290.

2-1-2. Characterization of the Reaction Products



Compound 19a': White solid; Mp 123–124 °C; IR (ATR) ν 1733, 1341, 1256, 1217, 1160, 1090, 1063, 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H), 2.36 (s, 3H), 2.39 (d, *J* = 1.2 Hz, 2H), 3.07 (s, 2H), 3.66 (s, 6H), 4.33 (d, *J* = 4.0 Hz, 2H), 5.31–5.34 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.4, 21.5, 32.2, 35.4, 45.2, 52.9 (2C), 53.8, 119.7, 124.5, 125.6, 127.4 (2C), 128.9 (2C), 129.3, 129.5, 130.2, 132.3, 134.4, 136.2, 143.3, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_6S^+$ ($M+Na^+$): 478.1295. Found: 478.1290.

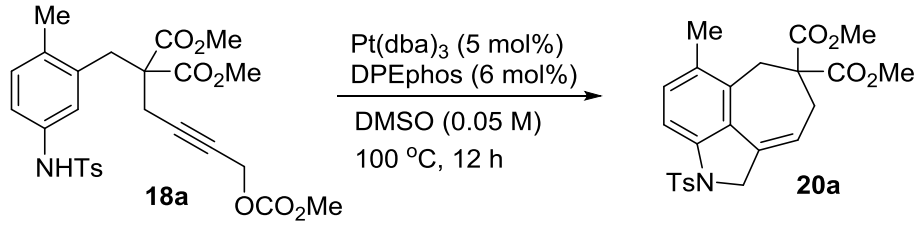


19a"

Compound 19a": Colorless oil; IR (ATR) ν 1731, 1318, 1256, 1216, 1158, 1092, 877, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 3H), 2.41 (s, 3H), 3.00 (t, *J* = 2.8 Hz, 2H), 3.09 (s, 2H), 3.71 (s, 6H), 5.11 (t, *J* = 2.8 Hz, 2H), 6.28 (br-s, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.5, 21.6, 32.8, 32.9, 52.9 (2C), 53.6, 78.9, 97.8, 124.1, 124.7, 127.2 (2C), 128.6, 129.6 (2C), 131.6, 132.1, 132.7, 136.7, 143.7, 170.9 (2C), 207.6; (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_6S^+$ ($M+Na^+$): 478.1295. Found: 478.1300.

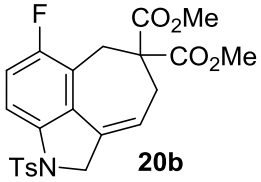
2-2. General Procedure for the Pt-Catalyzed Cascade Cyclization and Characterization of the Reaction Products

2-2-1. General Procedure for the Pt-Catalyzed Cascade Cyclization

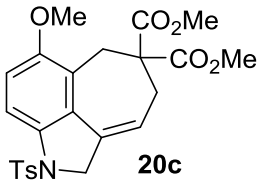


General Procedure: 18a (31.1 mg, 0.0585 mmol), $Pt(dba)_3$ (2.6 mg, 0.00207 mmol), and DPEphos (1.9 mg, 0.00248 mmol) were dissolved in DMSO (1.2 mL), and the resulting solution was stirred at 100 °C. After 6 h, the reaction was quenched with water, and the mixture was extracted with AcOEt/Hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1) to give **20a** (24.0 mg, 90% yield) as white solid.; Mp 138–139 °C; IR (ATR) ν 1730, 1436, 1348, 1233, 1166, 1046, 809, 681 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H), 2.36 (s, 3H), 2.86 (d, *J* = 3.6 Hz, 2H), 3.28 (s, 2H), 3.55 (s, 3H), 3.55 (s, 3H), 4.48 (d, *J* = 2.4 Hz, 2H), 5.56–5.59 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 19.6, 21.5, 35.4, 36.3, 52.6 (2C), 55.1, 55.6, 112.7, 117.1, 127.3 (2C), 127.6, 129.7 (2C), 131.3, 131.7, 132.3, 132.7, 133.8, 143.0, 144.0, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_6S^+$ ($M+Na^+$): 478.1295. Found: 478.1294.

2-2-2. Characterization of the Reaction Products

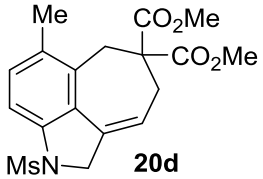


Compound 20b: Colorless oil; IR (ATR) ν 1732, 1444, 1354, 1235, 1164, 1140, 1090, 1058, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.89 (d, *J* = 2.0 Hz, 2H), 3.34 (s, 2H), 3.58 (s, 6H), 4.51 (d, *J* = 2.0 Hz, 2H), 5.61–5.62 (m, 1H), 6.90 (t, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.50 (dd, *J* = 4.2 Hz, 8.8 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 31.5 (d, *J* = 19.2 Hz), 36.0, 52.8 (2C), 54.6, 55.6, 113.8 (d, *J* = 38.0 Hz), 115.6 (d, *J* = 102.8 Hz), 118.4, 121.6 (d, *J* = 68.4 Hz), 127.2 (2C), 129.2, 129.7 (2C), 132.0, 133.5, 140.5, 144.3, 157.1 (d, *J* = 961.2 Hz), 170.6 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{22}FNNaO_6S^+$ ($M+Na^+$): 482.1044. Found: 482.1050.



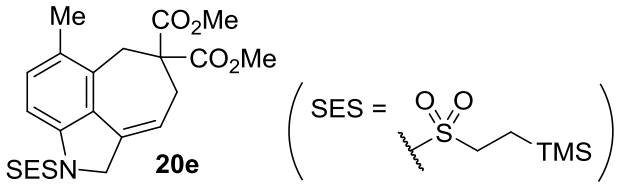
Compound 20c: Colorless oil; IR (ATR) ν 1723, 1438, 1351, 1255, 1162, 1090, 1062, 1019, 812 cm^{-1}; ^1H NMR

($CDCl_3$): δ 2.36 (s, 3H), 2.86 (d, *J* = 3.6 Hz, 2H), 3.36 (s, 2H), 3.55 (s, 6H), 3.81 (s, 3H), 4.46 (d, *J* = 2.0 Hz, 2H), 5.57–5.59 (m, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 32.2, 35.9, 52.6 (2C), 54.9, 55.5, 56.4, 111.4, 113.4, 117.8, 123.3, 127.3 (2C), 128.9, 129.6 (2C), 132.5, 133.6, 138.1, 143.9, 153.8, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_7S^+$ ($M+Na^+$): 494.1244. Found: 494.1225.



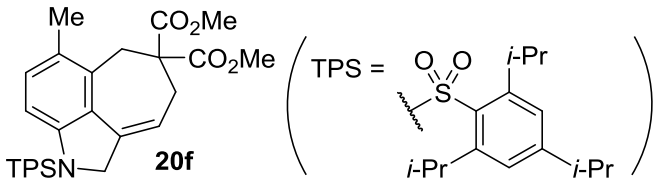
20d

Compound 20d: Colorless oil; IR (ATR) ν 1731, 1436, 1347, 1233, 1158, 1086, 961, 813, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.79 (s, 3H), 2.95–2.97 (m, 2H), 3.39 (s, 2H), 3.62 (s, 6H), 4.54 (dd, *J* = 2.8 Hz, 5.6Hz, 2H), 5.71–5.73 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 34.4, 35.5, 36.4, 52.7 (2C), 55.2, 56.1, 112.5, 117.8, 127.8, 131.4, 132.2, 132.3, 133.0, 142.9, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{18}H_{21}NNaO_6S^+$ ($M+Na^+$): 402.0982. Found: 402.0988.



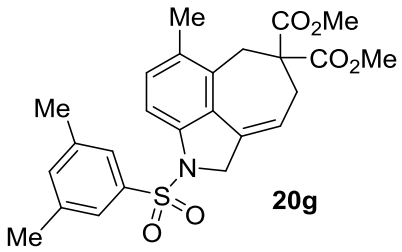
20e

Compound 20e: Colorless oil; IR (ATR) ν 1733, 1436, 1347, 1251, 1144, 1086, 842, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ –0.01 (s, 9H), 0.96–1.01 (m, 2H), 2.31 (s, 3H), 2.90–2.96 (m, 4H), 2.96 (s, 2H), 3.61 (s, 6H), 4.60 (dd, *J* = 2.8 Hz, 5.6 Hz, 2H), 5.67–5.70 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ −2.13 (3C), 9.46, 19.5, 35.5, 36.4, 45.5, 52.6 (2C), 55.3, 56.4, 112.0, 117.4, 127.6, 131.3, 131.4, 132.6, 132.9, 143.2, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{22}H_{31}NNaO_6SSi^+$ ($M+Na^+$): 488.1534. Found: 488.1540.



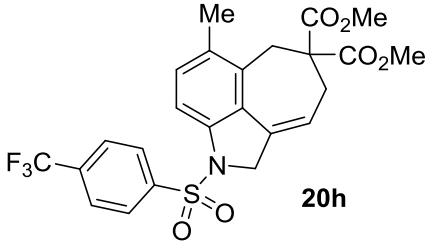
20f

Compound 20f: White solid; Mp 146–147 °C; IR (ATR) ν 1736, 1436, 1326, 1234, 1164, 1086, 755, 666; ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 6H), 1.17 (s, 6H), 1.25 (s, 3H), 1.27 (s, 3H), 2.28 (s, 3H), 2.87–2.93 (m, 3H), 3.35 (s, 1H), 3.59 (s, 6H), 4.14 (sept, *J* = 6.8 Hz, 2H), 4.42 (dd, *J* = 2.8 Hz, 5.6 Hz, 2H), 5.59–5.61 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 7.16 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 19.5, 23.5 (2C), 24.6 (4C), 29.3 (2C), 34.1, 35.6, 36.4, 52.6 (2C), 54.4, 55.2, 111.4, 116.9, 123.9 (2C), 126.6, 130.5, 131.1, 132.1, 132.5, 132.7, 144.0, 151.2 (2C), 153.4, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{32}H_{41}NNaO_6S^+$ ($M+Na^+$): 590.2547. Found: 590.2535.



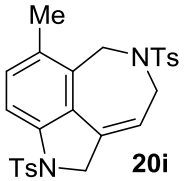
20g

Compound 20g: White solid; Mp 139–140 °C; IR (ATR) ν 1733, 1437, 1353, 1234, 1162, 1087, 753, 687; ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H), 2.31 (s, 6H), 2.88 (d, *J* = 3.6 Hz, 2H), 3.29 (s, 2H), 3.56 (s, 6H), 4.49 (d, *J* = 2.8 Hz, 2H), 5.58–5.60 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 7.38 (s, 2H), 7.41 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.5, 21.2 (2C), 35.5, 36.3, 52.6 (2C), 55.1, 55.6, 112.4, 117.0, 124.8 (2C), 127.4, 131.2, 131.7, 132.2, 132.7, 134.9, 136.6, 139.0 (2C), 143.0, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{25}H_{27}NNaO_6S^+$ (M+Na^+): 492.1451. Found: 492.1455.



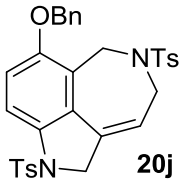
20h

Compound 20h: Colorless oil; IR (ATR) ν 1733, 1320, 1234, 1168, 1131, 1108, 1091, 1061, 754, 716; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 2.87 (dd, *J* = 3.2 Hz, 7.2 Hz, 2H), 3.29 (s, 2H), 3.53 (s, 6H), 4.53 (d, *J* = 2.4 Hz, 5.2 Hz, 2H), 5.60–5.63 (m, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 19.6, 35.4, 36.3, 52.6 (2C), 55.0, 55.8, 112.9, 117.8, 125.9 (q, *J* = 1097 Hz), 126.2 (q, *J* = 15.2 Hz, 2C), 127.7 (2C), 127.9, 131.4 (2C), 131.8, 132.5, 133.1, 134.7 (q, *J* = 131 Hz), 140.3, 142.2, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{22}F_3NNaO_6S^+$ (M+Na^+): 532.1012. Found: 532.1024.



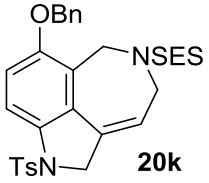
20i

Compound 20i: Colorless oil; IR (ATR) ν 1597, 1459, 1331, 1154, 1088, 928, 812, 752, 715; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 4.17 (dd, *J* = 2.6 Hz, 5.8 Hz, 2H), 4.26 (d, *J* = 3.6 Hz, 2H), 4.54 (s, 2H), 5.34–5.35 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 7.22–7.27 (m, 4H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.4, 21.5, 49.7, 50.8, 54.9, 112.9, 117.4, 126.9 (2C), 127.0, 127.2 (2C), 128.6 (2C), 129.8 (2C), 129.9, 131.9, 133.0, 133.3, 133.5, 136.3, 143.3, 143.4, 144.3; (+)-ESI-HRMS. Calcd for $C_{26}H_{26}N_2NaO_4S_2^+$ (M+Na^+): 517.1226. Found: 517.1230.



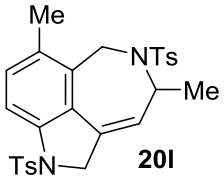
20j

Compound 20j: White solid; Mp 178–179 °C; IR (ATR) ν 1596, 1440, 1351, 1332, 1255, 1155, 1119, 1090, 1033, 760, 662; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.37 (s, 3H), 4.21 (s, 4H), 4.68 (s, 2H), 5.08 (s, 2H), 5.41–5.43 (m, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.34–7.44 (m, 6H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.4, 21.5, 47.4, 50.4, 54.9, 71.3, 113.5, 114.1, 118.2, 124.2, 127.1 (2C), 127.2 (2C), 127.5 (2C), 128.1, 128.3, 128.6 (2C), 128.7 (2C), 129.8 (2C), 133.5, 133.6, 136.5, 136.8, 138.9, 143.3, 144.3, 151.5; (+)-ESI-HRMS. Calcd for $C_{32}H_{30}N_2NaO_5S_2^+$ ($M+Na^+$): 609.1488. Found: 609.1475.



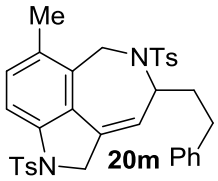
20k

Compound 20k: White solid; Mp 152–153 °C; IR (ATR) ν 1596, 1444, 1331, 1251, 1166, 1142, 1091, 843, 743; ^{1}H NMR ($CDCl_3$): δ –0.16 (s, 9H), 0.76–0.81 (m, 2H), 2.38 (s, 3H), 2.62–2.67 (m, 2H), 4.23 (d, *J* = 3.2 Hz, 2H), 4.48 (dd, *J* = 2.6 Hz, 5.4 Hz, 2H), 4.71 (s, 2H), 5.07 (s, 2H), 5.63–5.66 (m, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.31–7.44 (m, 5H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ –2.3 (3C), 10.0, 21.6, 46.7, 49.0, 50.1, 55.1, 71.2, 114.0, 114.5, 120.0, 125.5, 127.3 (2C), 127.4 (2C), 128.0, 128.3, 128.6 (2C), 129.8 (2C), 133.3, 133.4, 136.6, 139.1, 144.4, 151.2; (+)-ESI-HRMS. Calcd for $C_{30}H_{36}N_2NaO_5S_2Si^+$ ($M+Na^+$): 619.1727. Found: 619.1718.



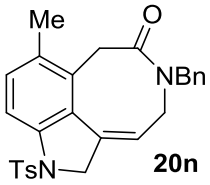
20l

Compound 20l: Colorless oil; IR (ATR) ν 1597, 1461, 1335, 1155, 1099, 813, 754, 679; ^{1}H NMR ($CDCl_3$): δ 1.28 (d, *J* = 6.8 Hz, 3H), 2.33 (s, 3H), 2.36 (s, 6H), 4.00 (d, *J* = 17.2 Hz, 1H), 4.10–4.19 (m, 2H), 4.82 (t, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 5.37–5.40 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.4, 21.6, 21.7, 42.3, 53.9, 55.0, 112.4, 122.8, 126.8 (2C), 127.1, 127.3 (2C), 128.4 (2C), 129.7 (2C), 129.9, 131.2, 131.6, 133.5, 134.0, 136.5, 143.2, 143.4, 144.2; (+)-ESI-HRMS. Calcd for $C_{27}H_{28}N_2NaO_4S_2^+$ ($M+Na^+$): 531.1383. Found: 531.1413.



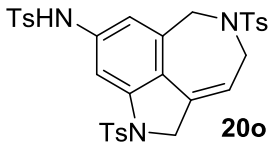
20m

Compound 20m: Colorless oil; IR (ATR) ν 1597, 1440, 1334, 1154, 1091, 812, 749, 680, 653; ^{1}H NMR ($CDCl_3$): δ 1.75–1.91 (m, 2H), 2.32 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 2.68–2.83 (m, 2H), 3.97 (d, *J* = 17.4 Hz, 1H), 4.05–4.13 (m, 2H), 4.70 (br-s, 1H), 5.03 (d, *J* = 17.4 Hz, 1H), 5.35–5.38 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.18–7.26 (m, 5H), 7.27–7.33 (m, 3H), 7.64 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.3, 21.5, 31.6, 36.9, 42.6, 55.0, 58.2, 112.4, 121.5, 126.0, 126.8 (2C), 127.0, 127.2 (2C), 128.2 (2C), 128.4 (2C), 128.4 (2C), 129.7 (2C), 130.0, 131.7, 131.7, 133.6, 133.6, 136.4, 141.2, 143.2, 143.5, 144.2; (+)-ESI-HRMS. Calcd for $C_{34}H_{34}N_2NaO_4S_2^+$ ($M+Na^+$): 621.1852. Found: 621.1852.



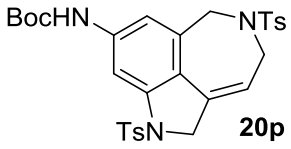
20n

Compound 20n: Colorless oil; IR (ATR) ν 1643, 1454, 1352, 1160, 1091, 812, 748, 658; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 2.49 (s, 3H), 3.94 (br-s, 2H), 4.02 (br-s, 2H), 4.35 (d, *J* = 2.0 Hz, 2H), 4.45 (br-s, 2H), 5.43–5.46 (m, 1H), 7.14–7.16 (m, 3H), 7.22–2.25 (m, 5H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 19.7, 21.6, 35.4, 46.2, 50.0, 57.3, 113.7, 117.2, 127.0, 127.4 (2C), 127.5, 128.2 (2C), 128.5 (2C), 129.7 (2C), 132.7, 132.9, 133.4, 133.5, 137.3, 137.4, 144.3, 144.4, 171.9; (+)-ESI-HRMS. Calcd for $C_{27}H_{26}N_2NaO_3S_2^+$ ($M+Na^+$): 481.1556. Found: 481.1556.



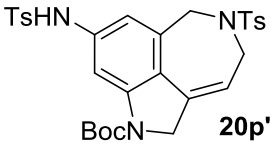
20o

Compound 4o: White solid; Mp 169–170 °C; IR (ATR) ν 1596, 1458, 1338, 1152, 1090, 1039, 1016, 899, 814 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H), 2.34 (s, 3H), 2.34 (s, 3H), 4.14 (br-s, 2H), 4.16 (s, 2H), 4.41 (s, 2H), 5.35 (br-s, 1H), 6.54 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H)7.57 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 10.57 (br-s, 1H); ^{13}C NMR (DMSO-d_6): δ 20.7, 21.0, 21.0, 50.2, 52.9, 54.7, 102.6, 112.2, 116.8, 121.8, 126.8 (2C), 126.9 (2C), 127.0 (2C), 128.3 (2C), 129.9 (2C), 130.0 (2C), 131.0, 132.9, 135.8, 136.0, 136.5, 139.3, 142.7, 143.6, 144.7, 144.8; (+)-ESI-HRMS. Calcd for $C_{32}H_{31}N_3NaO_6S_3^+$ ($M+Na^+$): 672.1267. Found: 672.1283.



20p

Compound 20p: White solid; Mp 133–134 °C; IR (ATR) ν 3353, 2978, 1725, 1538, 1494, 1424, 1226, 1056, 904, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (s, 9H), 2.35 (s, 3H), 2.37 (s, 3H), 4.16 (d, *J* = 2.8 Hz, 2H), 4.22 (d, *J* = 2.8 Hz, 2H), 4.51 (s, 2H), 5.20–5.24 (m, 1H), 6.73 (d, *J* = 1.6 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 7.12 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 1.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.3, 21.5, 28.3 (3C), 50.6, 53.9, 54.9, 81.1, 102.6, 111.7, 115.0, 121.4, 127.2 (2C), 127.3 (2C), 128.5 (2C), 129.8 (2C), 132.6, 133.6, 135.7, 136.3, 140.4, 143.3, 144.4, 145.7, 152.2; (+)-ESI-HRMS. Calcd for $C_{30}H_{33}N_3NaO_6S_2^+$ ($M+Na^+$): 618.1703. Found: 618.1703.

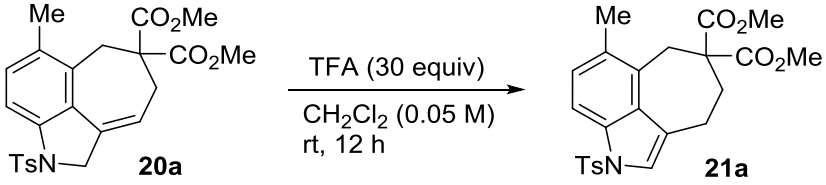


20p'

Compound 20p': White solid; Mp 117–118 °C; IR (ATR) ν 3253, 2979, 1703, 1599, 1470, 1047, 1017, 950, 902, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.53 (s, 9H), 2.20 (s, 3H), 2.35 (s, 3H), 4.11 (d, *J* = 2.4 Hz, 2H), 4.29 (d, *J* = 2.4 Hz, 2H), 4.55 (s, 2H), 5.23–5.27 (m, 1H), 6.62 (br-s, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.80 (br-s, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.29 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.1, 21.4, 28.4 (3C), 50.9, 53.8, 54.1, 83.2, 105.7, 112.3, 112.3, 115.6, 127.6 (2C), 127.6 (2C), 128.2 (2C), 128.2 (2C), 129.9, 135.4, 136.4, 137.0, 138.5, 138.5, 142.6, 144.2, 151.0; (+)-ESI-HRMS. Calcd for $C_{30}H_{33}N_3NaO_6S_2^+$ ($M+Na^+$): 618.1703. Found: 618.1688.

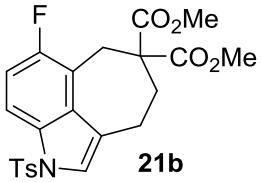
2-3. General Procedure for the Acid-Promoted Isomerization of 3,4-Fused Tricyclic 3-Alkylidene Indoline Derivatives and Characterization of the Reaction Products

2-3-1. General Procedure for the Acid-Promoted Isomerization of 3,4-Fused Tricyclic 3-Alkylidene Indoline Derivatives

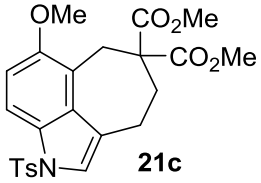


General Procedure: To a stirred solution of **20a** (45.6 mg, 0.100 mmol) in CH_2Cl_2 (3.3 mL) was added trifluoroacetic acid (TFA, 0.22 mL), and the resulting solution was stirred at room temperature. After 12 h, the reaction mixture was evaporated and the obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **21a** (45.0 mg, 99% yield) as white solid.; Mp 146–147 °C; IR (ATR) ν 1731, 1432, 1369, 1282, 1218, 1172, 1133, 1091, 664; ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.38 (s, 3H), 2.41–2.44 (m, 2H), 2.90–2.91 (m, 2H), 3.53 (s, 2H), 3.66 (s, 6H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.16 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.8, 21.5, 21.8, 31.6, 33.0, 52.7 (2C), 58.6, 112.0, 120.9, 124.5, 126.7 (2C), 127.8, 128.6, 129.8 (2C), 130.9, 131.2, 133.7, 135.4, 144.5, 172.2 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_6S^+$ ($M+Na^+$): 478.1295. Found: 478.1300.

2-3-2. Characterization of the Reaction Products

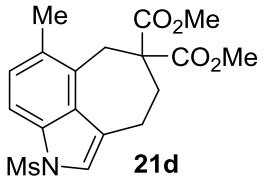


Compound 21b: White solid; Mp 125–126 °C; IR (ATR) ν 1731, 1433, 1360, 1221, 1172, 1134, 1088, 750, 664; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.43–2.45 (m, 2H), 2.88–2.91 (m, 2H), 3.54 (s, 2H), 3.68 (s, 6H), 6.94 (t, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.24 (s, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 28.5, 32.9, 52.8 (2C), 58.2, 112.9 (d, *J* = 49.6 Hz), 113.8 (d, *J* = 19.2 Hz), 116.5 (d, *J* = 72.4 Hz), 122.5, 124.2, 126.7 (2C), 129.9 (2C), 131.1, 131.7 (d, *J* = 23.2 Hz), 135.1, 144.9, 156.8 (d, *J* = 957.2 Hz), 171.9 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{22}FNNaO_6S^+$ ($M+Na^+$): 482.1044. Found: 482.1025.



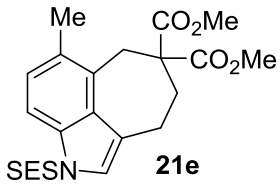
Compound 21c: White solid; Mp 107–108 °C; IR (ATR) ν 1731, 1430, 1356, 1255, 1218, 1169, 1134, 1087, 748, 663; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.42–2.45 (m, 2H), 2.86–2.88 (m, 2H), 3.57 (s, 2H), 3.64 (s, 6H), 3.83 (s,

3H), 6.88 (d, *J* = 9.0 Hz, 1H), 7.17 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.9, 28.8, 32.8, 52.6 (2C), 57.0, 58.5, 110.3, 112.5, 118.2, 122.1, 124.3, 126.7 (2C), 129.7 (2C), 129.7, 130.0, 135.3, 144.5, 153.4, 172.2 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{25}NNaO_7S^+$ ($M+Na^+$): 494.1244. Found: 494.1237.



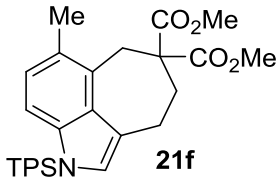
21d

Compound 21d: White solid; Mp 144–145 °C; IR (ATR) ν 1730, 1433, 1365, 1281, 1220, 1171, 1130, 1080, 960, 771; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 2.48–2.51 (m, 2H), 2.94–2.96 (m, 2H), 3.00 (s, 3H), 3.61 (s, 2H), 3.71 (s, 6H), 7.06 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 21.8, 31.7, 33.0, 40.1, 52.8 (2C), 58.6, 111.5, 120.9, 124.6, 128.1, 128.9, 131.2, 131.3, 133.8, 172.3 (2C); (+)-ESI-HRMS. Calcd for $C_{18}H_{21}NNaO_6S^+$ ($M+Na^+$): 402.0982. Found: 402.0979.



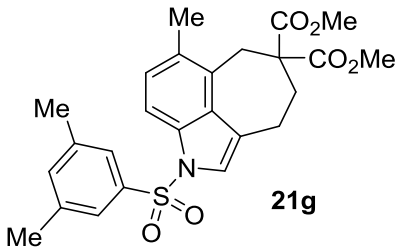
21e

Compound 21e: White solid; Mp 122–123 °C; IR (ATR) ν 1732, 1425, 1365, 1219, 1173, 1130, 1078, 843; ^{1}H NMR ($CDCl_3$): δ–0.04 (s, 9H), 0.82–0.87 (m, 2H), 2.44 (s, 3H), 2.47–2.51 (m, 2H), 2.94–2.97 (m, 2H), 3.07–3.12 (m, 2H), 3.63 (s, 2H), 3.68 (s, 6H), 7.07 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ −2.13 (3C), 9.88, 18.8, 21.9, 31.6, 33.1, 50.3, 52.7 (2C), 58.6, 111.5, 121.7, 123.1, 127.8, 128.8, 130.8, 131.0, 134.0, 172.3 (2C); (+)-ESI-HRMS. Calcd for $C_{22}H_{31}NNaO_6SSi^+$ ($M+Na^+$): 488.1534. Found: 488.1542.



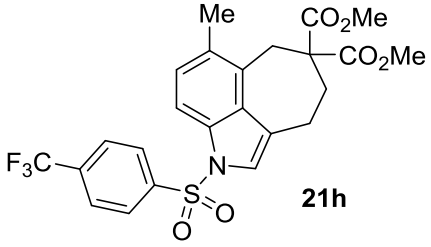
21f

Compound 21f: White solid; Mp 121–122 °C; IR (ATR) ν 1733, 1431, 1343, 1281, 1219, 1169, 1129, 1079, 661; ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 6H), 1.10 (s, 6H), 1.23 (s, 3H), 1.24 (s, 3H), 2.37 (s, 3H), 2.44–2.47 (m, 2H), 2.85–2.94 (m, 3H), 3.58 (s, 2H), 3.68 (s, 6H), 4.16 (sept, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.9, 23.5 (2C), 24.5 (4C), 29.3 (2C), 31.7, 33.3, 34.2, 52.7 (2C), 58.7, 110.9, 120.2, 122.6, 124.1 (2C), 127.4, 128.4, 130.0, 130.3, 131.9, 133.8, 151.2 (2C), 154.1, 172.3 (2C); (+)-ESI-HRMS. Calcd for $C_{32}H_{41}NNaO_6S^+$ ($M+Na^+$): 590.2547. Found: 590.2547.



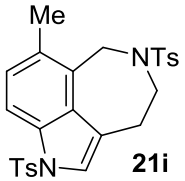
21g

Compound 21g: White solid; Mp 144–145 °C; IR (ATR) ν 1731, 1431, 1368, 1269, 1218, 1170, 1079, 755, 683; ^{1}H NMR ($CDCl_3$): δ2.31 (s, 6H), 2.39 (s, 3H), 2.42–2.25 (m, 2H), 2.90–2.93 (m, 2H), 3.54 (s, 2H), 3.66 (s, 6H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 7.17 (s, 1H), 7.44 (s, 2H), 7.63 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 21.2 (2C), 21.9, 31.6, 33.0, 52.7 (2C), 58.6, 111.9, 120.9, 124.2 (2C), 124.3, 127.7, 128.5, 130.8, 131.1, 133.6, 135.4, 138.1, 139.2 (2C), 172.3 (2C); (+)-ESI-HRMS. Calcd for $C_{25}H_{27}NNaO_6S^+$ ($M+Na^+$): 492.1451. Found: 492.1453.



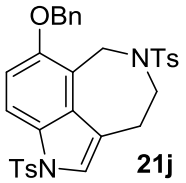
21h

Compound 21h: Colorless oil; IR (ATR) ν 1731, 1320, 1219, 1172, 1130, 1061, 909, 841, 731, 715; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 2.42–2.44 (m, 2H), 2.90–2.92 (m, 2H), 3.54 (s, 2H), 3.64 (s, 6H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.16 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.8, 21.6, 31.4, 32.8, 52.7 (2C), 58.5, 111.9, 120.7, 122.9 (q, *J* = 1091 Hz), 125.7, 126.3 (q, *J* = 14.0 Hz, 2C), 127.2 (2C), 128.2, 129.0, 131.4, 131.7, 133.7, 135.0 (q, *J* = 134 Hz), 141.5, 172.1 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{22}F_3NNaO_6S^+$ ($M+Na^+$): 532.1012. Found: 532.1019.



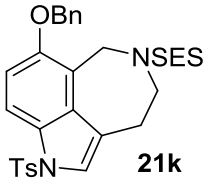
21i

Compound 21i: White solid; Mp 138–139 °C; IR (ATR) ν 1365, 1335, 1173, 1153, 1090, 810, 739, 664; ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 3.08 (t, *J* = 4.8 Hz, 2H), 3.64 (t, *J* = 4.8 Hz, 2H), 4.65 (s, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.30 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.1, 21.4, 21.6, 27.9, 49.0, 49.6, 112.1, 120.1, 122.8, 126.6 (2C), 126.7 (2C), 127.1, 129.0, 129.2, 129.4 (2C), 129.6, 129.9 (2C), 134.3, 135.1, 136.3, 143.2, 144.8; (+)-ESI-HRMS. Calcd for $C_{26}H_{26}N_2NaO_4S_2^+$ ($M+Na^+$): 517.1226. Found: 517.1212.



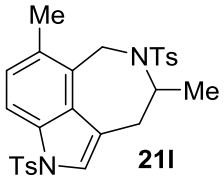
21j

Compound 21j: White solid; Mp 106–107 °C; IR (ATR) ν 1374, 1331, 1173, 1153, 1134, 1091, 748, 660; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.38 (s, 3H), 3.11 (t, *J* = 5.8 Hz, 2H), 3.58 (t, *J* = 5.8 Hz, 2H), 4.69 (s, 2H), 5.10 (s, 2H), 6.92 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.34–7.45 (m, 5H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.6, 28.9, 48.9, 49.4, 71.4, 110.5, 112.6, 119.8, 120.5, 124.1, 126.7 (2C), 126.9 (2C), 127.2 (2C), 127.9, 128.6 (2C), 129.6 (2C), 129.9 (2C), 130.0, 130.7, 135.0, 136.3, 137.2, 143.2, 144.6, 151.1; (+)-ESI-HRMS. Calcd for $C_{32}H_{30}N_2NaO_5S_2^+$ ($M+Na^+$): 609.1488. Found: 609.1475.



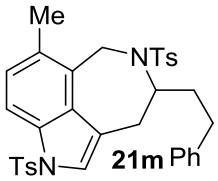
21k

Compound 21k: White solid; Mp 178–179 °C; IR (ATR) ν 1367, 1330, 1251, 1172, 1140, 1092, 838, 750, 665; ^{1}H NMR ($CDCl_3$): δ –0.13 (s, 9H), 0.82–0.87 (m, 2H), 2.35 (s, 3H), 2.77–2.81 (m, 2H), 3.12 (t, *J* = 5.6 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 4.82 (s, 2H), 5.11 (s, 2H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.32–7.43 (m, 6H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ –2.25 (3C), 10.1, 21.5, 28.9, 48.0, 48.4, 49.4, 71.3, 110.6, 112.7, 120.3, 120.5, 124.2, 126.7 (2C), 127.2 (2C), 127.9, 128.6 (2C), 129.9 (2C), 130.0, 130.7, 135.0, 137.0, 144.9, 150.9; (+)-ESI-HRMS. Calcd for $C_{30}H_{36}N_2NaO_5S_2Si^+$ ($M+Na^+$): 619.1727. Found: 619.1718.

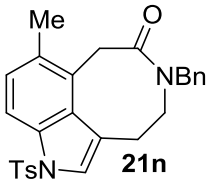


21l

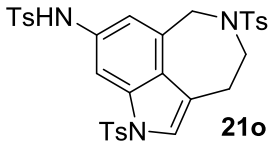
Compound 21l: White solid; Mp 157–158 °C; IR (ATR) ν 1368, 1334, 1276, 1156, 1136, 1087, 671, 659; ^{1}H NMR ($CDCl_3$): δ 1.39 (d, *J* = 6.4 Hz, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 2.80 (ddd, *J* = 1.6 Hz, 10.4 Hz, 15.6 Hz, 1H), 2.86 (dd, *J* = 6.0 Hz, 15.6 Hz, 1H), 4.29–4.39 (m, 1H), 4.47 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 16.8 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.94 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.2, 21.2, 21.5, 22.4, 33.0, 41.0, 55.1, 112.2, 119.3, 121.7, 125.6 (2C), 126.7 (2C), 127.1, 128.3 (2C), 129.6, 129.8, 129.8 (2C), 130.2, 133.5, 135.4, 136.5, 142.5, 144.8; (+)-ESI-HRMS. Calcd for $C_{27}H_{28}N_2NaO_4S_2^+$ ($M+Na^+$): 531.1383. Found: 531.1395.



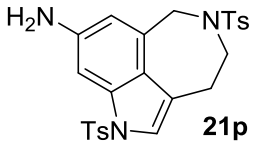
Compound 21m: White solid; Mp 149–150 °C; IR (ATR) ν 1370, 1333, 1173, 1153, 1134, 1090, 749, 671; ^{1}H NMR ($CDCl_3$): δ 1.91–1.99 (m, 1H), 2.02-2.11 (m, 1H), 2.29 (s, 3H), 2.32 (s, 3H), 2.41 (s, 3H), 2.77–2.86 (m, 3H), 2.96 (dd, *J* = 5.8 Hz, 15.4 Hz, 1H), 4.25–4.31 (m, 1H), 4.46 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.92 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.18–7.34 (m, 7H), 7.46 (d, *J* = 8.8 Hz, 1H) , 7.67 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.2, 21.3, 21.5, 31.3, 32.5, 38.1, 41.9, 58.7, 112.2, 119.0, 121.9, 125.5 (2C), 126.0, 126.6 (2C), 127.1, 128.2 (2C), 128.4 (2C), 128.5 (2C), 129.3, 129.8 (2C), 129.9, 130.2, 133.6, 135.4, 136.5, 141.5, 142.5, 144.8; (+)-ESI-HRMS. Calcd for $C_{34}H_{34}N_2NaO_4S_2^+$ ($M+Na^+$): 621.1852. Found: 621.1844.



Compound 21n: White amorphous; IR (ATR) ν 1643, 1453, 1367, 1174, 1092, 811, 730, 702, 664; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.57 (s, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 3.75 (t, *J* = 6.8 Hz, 2H), 4.08 (s, 2H), 4.46 (s, 2H), 6.99 (d, *J* = 7.2 Hz, 2H), 7.11–7.24 (m, 7H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.8, 21.5, 26.6, 35.7, 47.5, 51.0, 111.9, 118.6, 124.5, 126.8 (2C), 127.3, 127.7, 127.9, 128.0 (2C), 128.4 (2C), 129.4, 129.9 (2C), 131.5, 134.0, 135.2, 137.2, 144.9, 172.5; (+)-ESI-HRMS. Calcd for $C_{27}H_{26}N_2NaO_3S^+$ ($M+Na^+$): 481.1556. Found: 481.1543.



Compound 21o: White solid; Mp 193–194 °C; IR (ATR) ν 3261, 1597, 1446, 1368, 1336, 1091, 1066, 1016, 929, 910, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.38 (s, 3H), 2.38 (s, 3H), 3.04 (t, *J* = 5.2 Hz, 2 H), 3.55 (t, *J* = 5.2 Hz, 2H), 4.54 (s, 2H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.6, 21.6, 28.4, 49.7, 53.7, 104.9, 114.7, 119.9, 123.0, 126.0, 126.8 (2C), 126.9 (2C), 127.3(2C), 129.6 (2C), 129.8 (2C), 130.0 (2C), 133.0, 133.4, 134.7, 135.9, 135.9, 136.2, 143.4, 144.0, 145.1; (+)-ESI-HRMS. Calcd for $C_{32}H_{31}N_3NaO_6S_3^+$ ($M+Na^+$): 672.1267. Found: 672.1282.

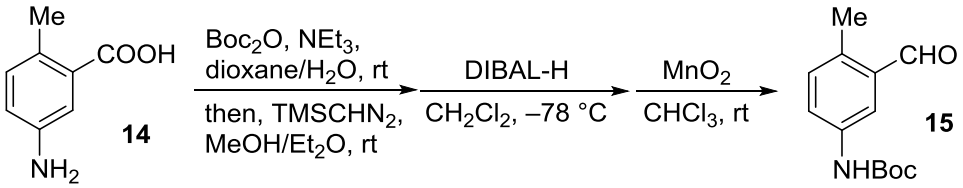


21p

Compound 21p: White solid; Mp 115–116 °C; IR (ATR) ν 2926, 1674, 1428, 1369, 1338, 1156, 1015, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 2.35 (s, 3H), 3.02 (t, *J* = 5.6 Hz, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 4.56 (s, 2H), 5.91 (br-s, 2H), 6.63 (s, 1H), 7.14 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.45 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.4, 21.5, 28.3, 49.7, 53.6, 101.3, 112.0, 120.3, 121.7, 123.8, 126.7 (2C), 126.8 (2C), 129.6 (2C), 129.9 (2C), 133.2, 134.9, 136.3, 136.3, 136.7, 143.3, 145.0; (+)-ESI-HRMS. Calcd for $C_{25}H_{25}N_3NaO_4S_2^+$ ($M+Na^+$): 518.1179. Found: 518.1179.

2-4. Substrate Syntheses and Compound Characterizations

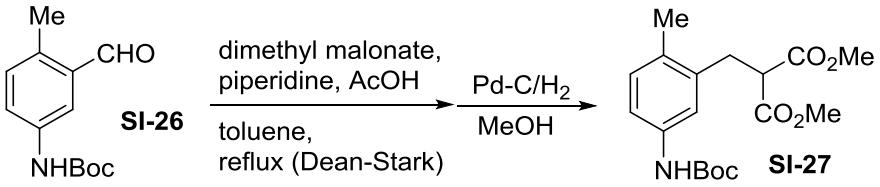
2-4-1. Synthesis of 18a–18i.



Compound 15: To a stirred solution of 3-amino-5-methyl-benzoic acid (**14:** 1.51 g, 10.0 mmol) and triethylamine (2.1 mL 15.0 mmol) in dioxane (27 mL) and water (13 mL) at room temperature was added di-*tert*-butyl dicarbonate (3.27 g, 15.0 mmol). The reaction mixture was stirred for 18 h at room temperature. After the solvent was evaporated under reduced pressure, 1N aq. HCl was added dropwise to the residue. The obtained precipitate was collected, washed with water, and dried *in vacuo* to give white solid, which was used for the next reaction. The obtained white solid was dissolved in diethyl ether (25 mL) and methanol (25 mL), and trimethylsilyl diazomethane (10 mL, 2M in Et_2O, 20 mmol) was added dropwise to the reaction at 0 °C. The resulting solution was stirred for 10 min at the same temperature, and then the solvent was evaporated under reduced pressure. The obtained crude material was used for the next reaction without purification.

The crude ester was dissolved in CH_2Cl_2 (50 mL), and DIBAL-H (25 mL, 1M solution in hexane, 25 mmol) was added to the solution at –78 °C. After the solution was stirred for 2.5 h at same temperature, and 30 min at 0 °C, the reaction was quenched by the addition of aq. 1M Rochelle salt. After being stirred for 1 h, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was utilized for the next reaction without purification.

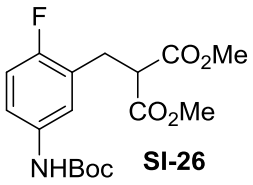
The crude alcohol was dissolved in $CHCl_3$ (20 mL), and MnO_2 (4.35 g, 50 mmol) was added to the solution. After being stirred for 24 h at room temperature, the reaction mixture was filtered through a short pad of celite, and the filtrate was concentrated *in vacuo*. The obtained residue was purified by recrystallization from hexane/AcOEt to provide benzaldehyde derivative **15** (1.53 g, 65% yield over 4 steps) as white solid. Mp 131 °C; IR (ATR) ν 3333, 2978, 1685, 1586, 1523, 1366, 1236, 1157, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.53 (s, 9H), 2.61 (s, 3H), 6.54 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 2.4 Hz, 8.0 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 10.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 28.3 (3C), 80.9, 121.5, 123.7, 132.4, 134.4, 135.0, 136.9, 152.7, 192.4.



Compound 16: Benzaldehyde **15** (1.53 g, 6.50 mmol), dimethyl malonate (0.82 mL, 7.15 mmol), piperidine (0.64 mL, 6.50 mmol), and acetic acid (35 μL, 0.65 mmol) were dissolved in toluene (22 mL) in a reaction vessel equipped with a Dean-Stark apparatus, and the solution was refluxed for 3 h. After cooling down to room temperature, the reaction mixture was evaporated *in vacuo*, and the obtained mixture was passed through a short

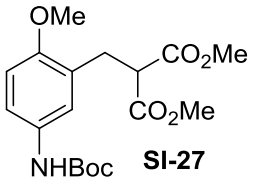
pad of silica to remove polar compounds (eluting with hexane/AcOEt = 4/1). The obtained crude residue was utilized for the next reaction. A suspension of the crude product and 5% Pd-C (188 mg) in MeOH (27 mL) was stirred at room temperature under a hydrogen atmosphere. After 5 h, the reaction mixture was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. The obtained residue was purified by flash column chromatography (hexane/AcOEt = 10/1) to give **16** (1.88 g, 83% yield) as white solid. Mp 88 °C; IR (ATR) ν 3372, 2954, 1722, 1523, 1231, 1153, 1055, 1024 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.27 (s, 3H), 3.19 (d, *J* = 8.0 Hz, 2H), 3.66 (t, *J* = 8.0 Hz, 1H), 3.71 (s, 6H), 6.43 (s, 1H), 7.06–7.08 (m, 2H), 7.18–7.20 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 18.5, 28.3 (3C), 32.0, 52.1, 52.6 (2C), 80.3, 117.2, 119.3, 130.7, 130.9, 136.3, 136.4, 152.7, 169.3 (2C); (+)-ESI-HRMS. Calcd for $C_{18}H_{25}NNaO_6^+$ 374.1574 ($M+Na^+$) found 374.1589.

Compounds **SI-28** and **SI-29** were also prepared according to the experimental procedures described above.



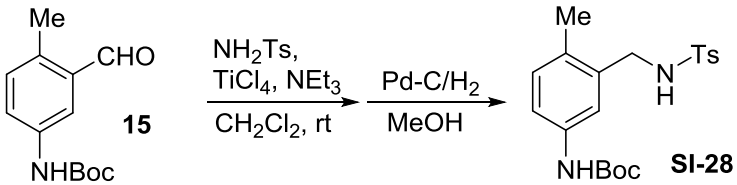
SI-26

Compound SI-26: Amorphous; IR (ATR) ν 3368, 2955, 1722, 1540, 1505, 1234, 1153, 1109 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 3.21 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 6H), 3.73 (t, *J* = 8.0 Hz, 1H), 6.39 (s, 1H), 6.92–6.96 (m, 1H), 7.14–7.16 (m, 1H), 7.24–7.26 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 28.6, 51.8, 52.6 (2C), 80.6, 115.6 (d, *J* = 22.9 Hz), 118.9, 121.3, 124.9 (d, *J* = 17.2 Hz), 134.3, 152.7, 157.0 (d, *J* = 244 Hz), 169.0 (2C); (+)-ESI-HRMS. Calcd for $C_{17}H_{22}FNNaO_6^+$ 378.1323 ($M+Na^+$) found 378.1334.



SI-27

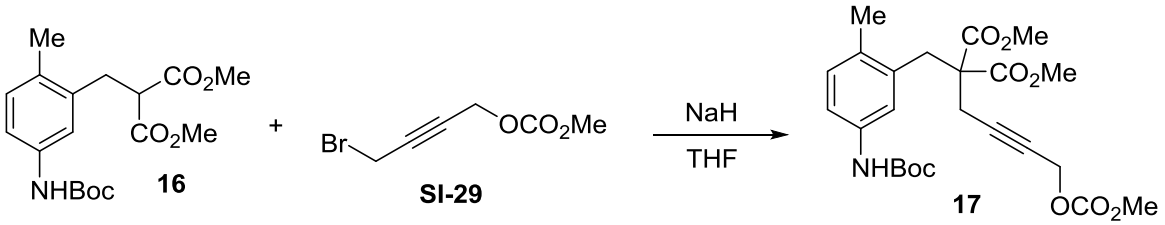
Compound SI-27: White solid; Mp 108 °C; IR (ATR) ν 3372, 2954, 1718, 1565, 1223, 1153, 1122, 1023 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 3.16 (d, *J* = 8.0 Hz, 2H), 3.69 (s, 6H), 3.79 (s, 3H), 3.83 (t, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 7.31 (dd, *J* = 2.8 Hz, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 30.2, 31.3, 52.4 (2C), 55.5, 80.2, 110.6, 118.8, 122.1, 126.3, 131.1, 153.0, 153.6, 169.5 (2C); (+)-ESI-HRMS. Calcd for $C_{18}H_{25}NNaO_7^+$ 390.1523 ($M+Na^+$) found 390.1478.



SI-28

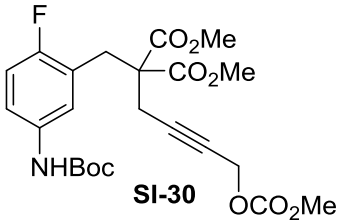
Compound SI-28: To a stirred solution of **15**, *p*-$TsNH_2$ (1.88 g, 11 mmol), and NEt_3 (4.18 mL, 30 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added $TiCl_4$ (0.55 mL, 5 mmol), and the resulting suspension was stirred at room

temperature. After 16 h, ethyl acetate was added to the reaction, and the resulting suspension was filtered through a short pad of celite. After evaporation *in vacuo*, the obtained crude residue was utilized for the next reaction. A suspension of the crude product and 5% Pd-C (188 mg) in MeOH (27 mL) was stirred at room temperature under a hydrogen atmosphere. After 5 h, the reaction mixture was filtered through a short pad of celite, and the filtrate was concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (hexane/AcOEt = 10/1) to give **SI-30** (1.88 g, 83% yield) as white solid. Mp 117 °C; IR (ATR) ν 3349, 2978, 1699, 1521, 1319, 1238, 1153, 1092, 1056 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (s, 9H), 2.20 (s, 3H), 2.44 (s, 3H), 4.03 (d, *J* = 5.6 Hz, 2H), 4.60 (t, *J* = 5.6 Hz, 1H), 6.41 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.09–7.16 (m, 2H), 7.29–7.32 (m, 2H), 7.74–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 18.1, 21.5, 28.3 (3C), 45.5, 80.5, 118.2, 119.0, 127.2 (2C), 129.7 (2C), 131.0, 131.2, 134.5, 136.4, 136.6, 143.5, 152.8; (+)-ESI-HRMS. Calcd for $C_{20}H_{26}N_2NaO_4S^+$ 413.1505 ($M+Na^+$) found 413.1491.



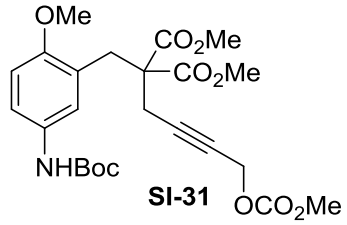
Compound 17: To a stirred solution of **16** (596 mg, 1.77 mmol) in THF (6 mL) at 0 °C was added NaH (60% oil. 85 mg, 2.12 mmol), and the resulting mixture was kept stirring at the same temperature. After 15 min, a THF solution of **SI-29** (439 mg, 6 mmol in 3 mL of THF) was added to the reaction, and the reaction was stirred for 16 h at room temperature. After dilution with AcOEt, the reaction was quenched with 1 M aq. HCl solution, washed with brine, dried over Na_2SO_4, and then evaporated *in vacuo*. The obtained crude residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **17** (659 mg, 80% yield) as white solid.; Mp 106–107 °C; IR (ATR) ν 1729, 1524, 1443, 1261, 1231, 1200, 1154, 1045, 950; ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.21 (s, 3H), 2.74 (t, *J* = 2.0 Hz, 2H), 3.39 (s, 2H), 3.76 (s, 6H), 3.83 (s, 3H), 4.73 (t, *J* = 2.0 Hz, 2H), 6.60 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.8, 22.8, 28.3 (3C), 34.1, 52.9 (2C), 55.2, 55.9, 58.0, 77.5, 80.1, 83.6, 117.3, 120.2, 131.1, 131.7, 134.1, 136.3, 152.7, 155.3, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{31}NNaO_9S^+$ ($M+Na^+$): 500.1891. Found: 500.1892.

Reference for Compound **SI-29**: *Org. Biomol. Chem*. **2012**, *10*, 2164.



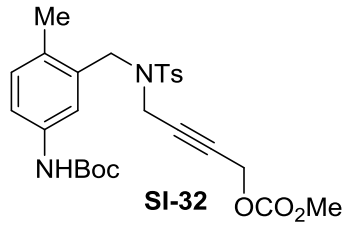
SI-30 was prepared from **SI-26** and **SI-29** according to the general procedure. White solid; Mp 107–108 °C; IR (ATR) ν 1725, 1536, 1505, 1443, 1263, 1205, 1155, 1112, 1048, 951; ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.70 (t, *J* = 2.4 Hz, 2H), 3.39 (s, 2H), 3.77 (s, 6H), 3.86 (s, 3H), 4.75 (t, *J* = 2.4 Hz, 2H), 6.91 (t, *J* = 9.2 Hz, 1H), 6.96 (s, 1H), 7.24 (dd, *J* = 2.8 Hz, 6.4 Hz, 1H) 7.54 (br-s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.7, 28.3 (3C), 31.6, 53.0 (2C), 55.2, 55.9,

56.9, 77.7, 80.3, 83.1, 115.3, 115.6, 119.0 (d, J = 22.8 Hz), 122.2 (d, J = 72.4 Hz), 134.6, (d, J = 76.0 Hz), 152.8, 155.5, 157.1 (d, J = 961 Hz), 170.0 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{28}FNNaO_9S^+$ ($M+Na^+$): 504.1640. Found: 504.1642.



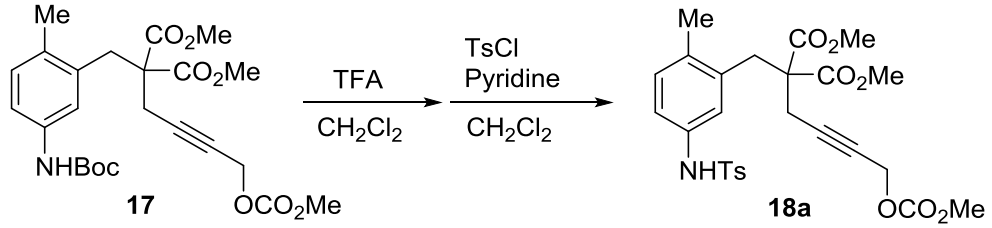
SI-31

SI-31 was prepared from **SI-27** and **SI-29** according to the general procedure. White solid; Mp 107–108 °C; IR (ATR) ν 1737, 1507, 1443, 1368, 1269, 1160, 1131, 1025, 951; ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.66 (s, 2H), 3.38 (s, 2H), 3.70 (s, 3H), 3.75 (s, 6H), 3.86 (s, 2H), 4.75 (s, 2H), 6.74 (d, J = 8.8 Hz, 1H), 6.81 (br-s, 1H), 7.06 (br-s, 1H), 7.15 (s, 1H) 7.51 (br-s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.9, 28.3 (3C), 32.3, 52.7 (2C), 55.2, 55.5, 56.0, 57.0, 77.1, 79.9, 83.7, 110.6, 118.7, 122.9, 123.9, 131.4, 153.0, 153.8, 155.5, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{31}NNaO_{10}S^+$ ($M+Na^+$): 516.1840. Found: 516.1847.



SI-32

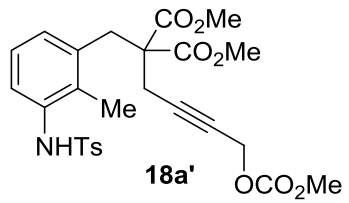
SI-32 was prepared from **SI-28** and **SI-2** according to the general procedure. White solid; Mp 90–91 °C; IR (ATR) ν 1751, 1723, 1524, 1445, 1347, 1263, 1157, 1092, 956, 903; ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9H), 2.33 (s, 3H), 2.46 (s, 3H), 3.82 (s, 3H), 3.90 (t, J = 2.0 Hz, 2H), 4.28 (s, 2H), 4.43 (t, J = 2.0 Hz, 2H), 6.62 (s, 1H), 7.08 (s, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.3, 21.5, 28.3 (3C), 35.8, 48.5, 55.2, 55.2, 79.8, 80.0, 80.3, 118.5, 120.4, 128.0 (2C), 129.5 (2C), 131.2, 132.3, 132.4, 135.1, 136.4, 143.8, 152.7, 155.3; (+)-ESI-HRMS. Calcd for $C_{26}H_{32}N_2NaO_7S^+$ ($M+Na^+$): 539.1822. Found: 539.1812.



17 **18a**

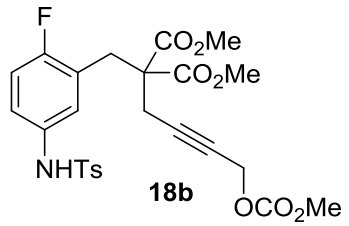
To a stirred solution of **17** (659 mg, 1.42 mmol) in CH_2Cl_2 (11.4 mL) at room temperature was added trifluoroacetic acid (TFA, 2.89 mL), and the resulting solution was stirred at the same temperature. After 30 min, the reaction was quenched with saturated aq. $NaHCO_3$ at 0 °C and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was

used for the next reaction without further purification. To a stirred solution of crude aniline and pyridine (0.13 mL, 1.56 mmol) in CH_2Cl_2 was added TsCl (298 mg, 1.56 mmol) at 0 °C. After the solution was stirred for 1 h at the same temperature, the reaction was quenched by the addition of 1N aq. HCl and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained crude residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 4/1) to give **18a** (669 mg, 91% yield) as white solid.; Mp 93–94 °C; IR (ATR) ν 1752, 1710, 1266, 1203, 1155, 816, 661 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.38 (s, 3H), 2.47 (t, *J* = 2.0 Hz, 2H), 3.30 (s, 2H), 3.73 (s, 6H), 3.91 (s, 3H), 4.70 (t, *J* = 2.0 Hz, 2H), 6.96–7.09 (m, 4H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.6, 21.5, 22.5, 34.1, 52.9 (2C), 55.6, 55.9, 57.3, 78.0, 83.4, 120.7, 124.3, 127.2 (2C), 129.5 (2C), 131.5, 134.3, 134.4, 134.5, 135.9, 143.6, 155.7, 170.2 (2C); (+)-ESI-HRMS. Calcd for $C_{26}H_{29}NNaO_9S^+$ ($M+Na^+$): 554.1455. Found: 554.1446.



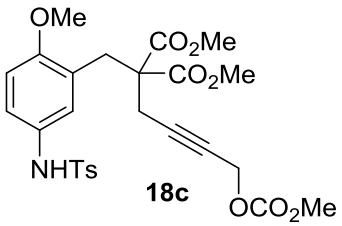
18a'

Compound 18a': White solid; Mp 110–111 °C; IR (ATR) ν 1735, 1261, 1206, 1160, 1092, 949, 911 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.40 (s, 3H), 2.57 (t, *J* = 2.0 Hz, 2H), 3.37 (s, 2H), 3.70 (s, 6H), 3.82 (s, 3H), 4.69 (t, *J* = 2.0 Hz, 2H), 6.35 (br-s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.8, 21.5, 22.6, 34.4, 52.8 (2C), 55.1, 55.7, 58.2, 77.3, 83.1, 124.5, 126.2, 127.1 (2C), 129.0, 129.6 (2C), 132.0, 135.0, 135.1, 136.5, 143.8, 155.1, 170.0 (2C); (+)-ESI-HRMS. Calcd for $C_{26}H_{29}NNaO_9S^+$ ($M+Na^+$): 554.1455. Found: 554.1452.

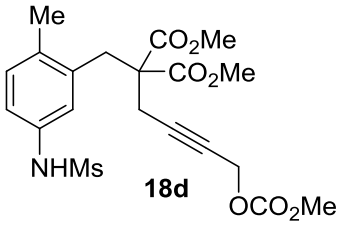


18b

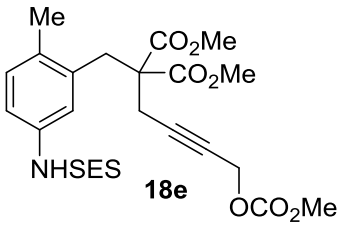
Compound 18b: Colorless oil; IR (ATR) ν 1732, 1442, 1262, 1202, 1161, 1091, 948, 791, 753, 664 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H), 2.44 (t, *J* = 2.4 Hz, 2H), 3.29 (s, 2H), 3.75 (s, 6H), 3.94 (s, 3H), 4.70 (t, *J* = 2.4 Hz, 2H), 6.89 (t, *J* = 9.2 Hz, 1H), 7.09 (dd, *J* = 2.8 Hz, 6.4 Hz, 1H) 7.22 (d, *J* = 8.0 Hz, 2H), 7.25–7.32 (m, 2H) 7.59 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 22.4, 31.5, 53.0 (2C), 55.7, 55.9, 56.5, 78.1, 82.9, 116.0 (d, *J* = 95.2 Hz,) 122.8 (d, *J* = 34.2 Hz), 122.9, 126.3 (d, *J* = 20.0 Hz), 127.2 (2C), 129.6 (2C), 132.8 (d, *J* = 11.6 Hz), 135.6, 143.8, 155.9, 158.9 (d, *J* = 973 Hz), 170.2 (2C); (+)-ESI-HRMS. Calcd for $C_{25}H_{26}FNNaO_9S^+$ ($M+Na^+$): 558.1205. Found: 558.1207.



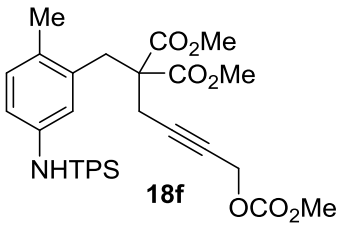
Compound 18c: White amorphous; IR (ATR) ν 1732, 1260, 1208, 1183, 1157, 1130, 948, 751, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.39 (t, *J* = 2.2 Hz, 2H), 3.26 (s, 2H), 3.68 (s, 3H), 3.73 (s, 6H), 3.92 (d, *J* = 1.6 Hz, 3H), 4.68 (t, *J* = 2.2 Hz, 2H), 6.69 (dd, *J* = 1.6 Hz, 8.8 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.06 (br-s, 1H) 7.21 (d, *J* = 8.8 Hz, 2H), 7.23–7.25 (m, 1H) 7.56 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 22.6, 32.1, 52.7 (2C), 55.4, 55.6, 56.0, 56.5, 77.4, 83.5, 110.7, 123.3, 123.3, 124.1, 127.2 (2C), 129.2, 129.5 (2C), 135.8, 143.4, 155.7, 155.8, 170.3 (2C); ESI-HRMS. Calcd for $C_{26}H_{29}NNaO_{10}S^{+}$ ($M+Na^{+}$): 570.1404. Found: 570.1409.



Compound 18d: White solid; Mp 96–97 °C; IR (ATR) ν 1732, 1442, 1324, 1260, 1201, 1149, 1046, 949, 792, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.71 (t, *J* = 2.2 Hz, 2H), 2.98 (s, 3H), 3.42 (s, 2H), 3.77 (s, 6H), 3.86 (s, 3H), 4.73 (t, *J* = 2.2 Hz, 2H), 6.91 (s, 1H), 7.08–7.13 (m, 2H), 7.17 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 18.7, 22.8, 34.2, 39.0, 53.0 (2C), 55.5, 55.9, 57.6, 78.0, 83.4, 119.5, 122.8, 131.8, 134.4, 134.8, 135.0, 155.6, 170.3 (2C); (+)-ESI-HRMS. Calcd for $C_{20}H_{25}NNaO_9S^{+}$ ($M+Na^{+}$): 478.1142. Found: 478.1153.

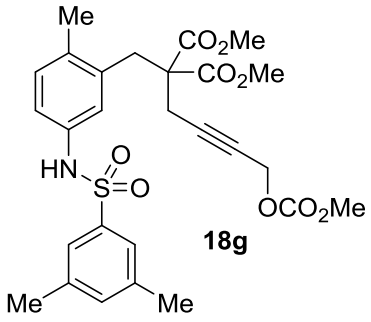


Compound 18e: Colorless oil; IR (ATR) ν 1736, 1262, 1216, 1146, 948, 842, 791, 751, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ –0.15 (s, 9H), 0.97–1.02 (m, 2H), 2.22 (s, 3H), 2.69 (t, *J* = 2.4 Hz, 2H), 2.98 (s, 2H), 3.41 (s, 2H), 3.77 (s, 6H), 3.86 (s, 3H), 4.73 (t, *J* = 2.4 Hz, 2H), 6.96 (s, 1H), 7.06–7.13 (m, 3H); ^{13}C NMR ($CDCl_3$): δ –2.1 (3C), 10.4, 18.7, 22.7, 34.1, 47.1, 53.0 (2C), 55.4, 55.8, 57.6, 78.0, 83.4, 118.8, 122.1, 131.8, 133.8, 134.9, 135.0, 155.5, 170.2 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{35}NNaO_9SSi^{+}$ ($M+Na^{+}$): 564.1694. Found: 564.1700



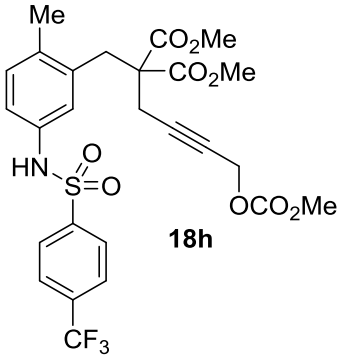
18f

Compound 18f: Colorless oil; IR (ATR) ν 1738, 1443, 1262, 1216, 1151, 950, 755, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (d, *J* = 3.2 Hz, 12H), 1.23 (d, *J* = 3.2 Hz, 6H), 2.15 (s, 3H), 2.71 (t, *J* = 2.4 Hz, 2H), 2.87 (q, *J* = 3.2 Hz, 2H), 3.33 (s, 2H), 3.71 (s, 6H), 3.87 (s, 3H), 4.08 (q, *J* = 3.2 Hz, 1H), 4.70 (t, *J* = 2.2 Hz, 2H), 6.83–6.86 (m, 2H), 6.94–6.97 (m, 2H), 7.12 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 18.8, 22.7, 23.5 (2C), 24.7 (4C), 29.8 (2C), 34.0, 34.1, 52.9 (2C), 55.4, 55.8, 57.6, 77.7, 83.4, 120.6, 123.7, 124.9 (2C), 131.3, 132.4, 134.4, 134.4, 134.7, 150.5 (2C), 152.8, 155.5, 170.2 (2C); (+)-ESI-HRMS. Calcd for $C_{34}H_{45}NNaO_9S^+$ ($M+Na^+$): 666.2707. Found: 666.2723.



18g

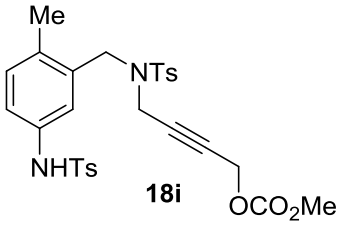
Compound 18g: White amorphous; IR (ATR) ν 1735, 1270, 1214, 1154, 746, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.31 (s, 6H), 2.47 (t, *J* = 2.0 Hz, 2H), 3.30 (s, 2H), 3.73 (s, 6H), 3.91 (s, 2H), 4.70 (t, *J* = 2.0 Hz, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.98 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 2.4 Hz, 8.4 Hz, 2H), 7.13 (s, 1H), 7.32 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 18.5, 21.1 (2C), 22.5, 34.0, 52.9 (2C), 55.6, 55.8, 57.3, 78.0, 83.4, 121.0, 124.4, 124.7 (2C), 131.4, 134.3, 134.3, 134.5, 134.5, 138.5, 139.0 (2C), 155.7, 170.1 (2C); (+)-ESI-HRMS. Calcd for $C_{27}H_{31}NNaO_9S^+$ ($M+Na^+$): 568.1612. Found: 568.1614.



18h

Compound 18h: Colorless oil; IR (ATR) ν 1733, 1321, 1263, 1163, 1131, 1061, 755, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.44 (t, *J* = 2.4 Hz, 2H), 3.30 (s, 2H), 3.73 (s, 6H), 3.91 (s, 2H), 4.69 (t, *J* = 2.4 Hz, 2H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 2.4 Hz, 8.4 Hz, 2H), 7.29 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.5, 22.6, 34.1, 53.0 (2C), 55.6, 55.9, 57.1, 78.1, 83.4, 120.8 (q, *J* = 805

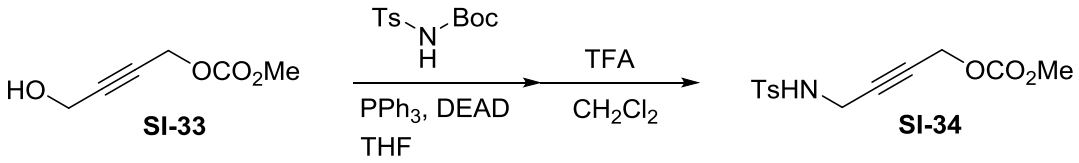
Hz), 121.0, 124.6, 126.1 (q, J = 15.6 Hz, 2C), 127.7 (2C), 131.7, 133.8, 134.4 (q, J = 134 Hz), 134.7, 135.0, 142.4, 155.8, 170.1 (2C); (+)-ESI-HRMS. Calcd for $C_{26}H_{26}F_3NNaO_9S^+$ (M+Na^+): 608.1173. Found: 608.1181.



18i

Compound 18i: Colorless oil; IR (ATR) ν 1753, 1445, 1328, 1266, 1160, 1092, 904, 816 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 3.69 (s, 2H), 3.86 (s, 3H), 4.18 (s, 2H), 4.40 (s, 2H), 6.91 (d, J = 2.4 Hz, 1H), 7.04 (br-s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.3, 21.5, 21.5, 35.6, 48.2, 55.1, 55.4, 79.7, 80.0, 121.6, 123.6, 127.2 (2C), 128.0 (2C), 129.5 (2C), 129.5 (2C), 131.6, 132.8, 134.5, 134.8, 135.1, 135.9, 143.7, 143.9, 155.3; (+)-ESI-HRMS. Calcd for $C_{28}H_{30}N_2NaO_7S_2^+$ (M+Na^+): 593.1387. Found: 593.1372.

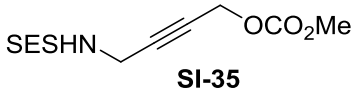
2-4-2. Synthesis of 18j–m, 18o, and 18p.



SI-33 **SI-34**

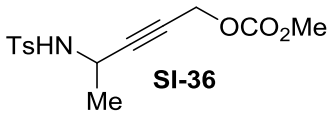
Compound SI-33: To a stirred solution of **SI-34** (148 mg, 1.03 mmol), *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (334 mg, 1.23 mmol) and PPh_3 (278 mg, 1.23 mmol) in THF (3.4 mL) at 0 °C was added diethyl azodicarboxylate (DEAD, 2.2 M solution in toluene, 0.56 mL, 1.23 mmol), and the resulting mixture was stirred at room temperature for 1 h. After evaporation, the crude mixture was filtered through a short pad of silica gel and the obtained residue was used for the next reaction without further purification. To a stirred solution of the crude sample in CH_2Cl_2 (8.0 mL) at room tenperature was added trifluoroacetic acid (2.0 mL), and the resulting solution was stirred at the same temperature. After 1 h, the reaction mixture was evaporated *in vacuo* and the obtained residue was purified by flash column chromatography (SiO_2, $CHCl_3$/AcOEt = 30/1) to give **SI-33** (252 mg, 85% yield) as white solid.; Mp 50–51 °C; IR (ATR) ν 1749, 1444, 1329, 1262, 1156, 1092, 1059, 949, 814; ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.80 (s, 3H), 3.87 (dt, J = 2.0 Hz, 6.0 Hz, 2H), 4.50 (t, J = 2.0 Hz, 2H), 4.85 (br-s, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 33.0, 55.1, 55.1, 78.1, 81.7, 127.4 (2C), 129.6 (2C), 136.5, 143.8, 155.0; (+)-ESI-HRMS. Calcd for $C_{13}H_{15}NNaO_5S^+$ (M^+Na^+): 320.0563. Found: 320.0565.

Reference for Compound **SI-33**: *J. Am. Chem. Soc.* **2003**, *125*, 4874.



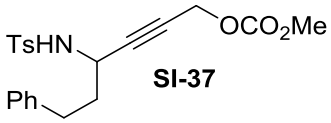
SI-35

SI-35 was prepared from the corresponding sulfonamide derivative (*J. Org. Chem*. **1993**, *58*, 2900.). White solid; Mp 99–100 °C; IR (ATR) ν 3304, 2983, 1613, 1593, 1493, 1382, 1018, 932, 825 cm-1; ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 9H), 1.05–1.09 (m, 2H), 3.03–3.07 (m, 2H), 3.82 (s, 3H), 4.01 (dt, *J* = 2.0 Hz, 6.0 Hz, 2H), 4.53 (br-s, 1H), 4.74 (t, *J* = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ –2.06 (3C), 10.4, 32.9, 49.8, 55.2, 55.3, 78.0, 82.8, 155.1; (+)-ESI-HRMS. Calcd for $C_{11}H_{21}NNaO_5SSi^+$ (M^+Na^+): 330.0802. Found: 330.0809.



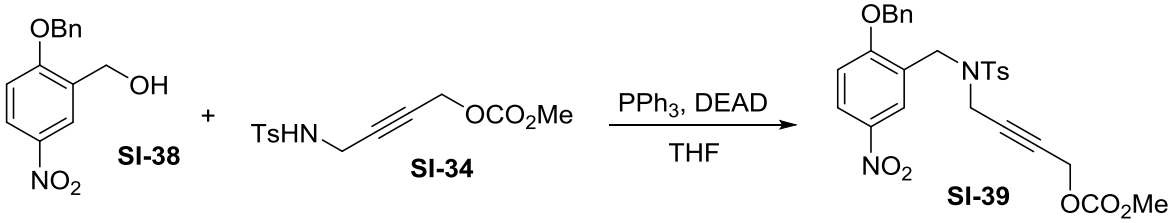
SI-36

SI-36 was prepared from the corresponding alcohol derivative (*Helv. Chim. Acta.* **1997**, *80*, 623.). White solid; Mp 91–92 °C; IR (ATR) ν 1750, 1444, 1332, 1262, 1155, 1089, 1022, 938, 815; ^{1}H NMR ($CDCl_3$): δ 1.41 (d, *J* = 6.8 Hz, 3H), 2.43 (s, 3H), 3.80 (s, 3H), 4.19–4.27 (m, 1H), 4.43 (d, *J* = 1.2 Hz, 2H), 4.56–4.67 (m, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 23.0, 41.3, 55.1, 55.1, 77.2, 86.2, 127.4 (2C), 129.5 (2C), 137.1, 143.7, 155.0; (+)-ESI-HRMS. Calcd for $C_{14}H_{17}NNaO_5S^+$ ($M+Na^+$): 334.0720. Found: 334.0732.



SI-37

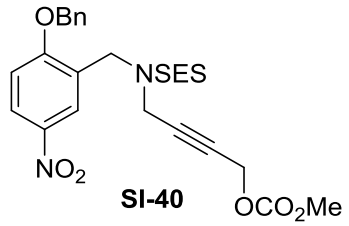
SI-37 was prepared from the corresponding alcohol derivative (*J. Am. Chem. Soc.* **2010**, *132,* 11926.). White solid; Mp 97–98 °C; IR (ATR) ν 1753, 1444, 1374, 1334, 1264, 1159, 1068, 952, 814; ^{1}H NMR ($CDCl_3$): δ 1.91–2.01 (m, 2H), 2.42 (s, 3H), 2.72 (t, *J* = 7.6 Hz, 2H), 3.79 (s, 3H), 4.06-4.13 (m, 1H), 4.43 (d, *J* = 1.8 Hz, 2H), 4.80 (br-s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.25–7.30 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 31.4, 37.7, 45.1, 55.1, 55.1, 78.2, 85.1, 126.2, 127.4 (2C), 128.5 (2C), 128.5 (2C), 129.5 (2C), 137.0, 140.3, 143.6, 155.0; (+)-ESI-HRMS. Calcd for $C_{21}H_{23}NNaO_5S^+$ ($M+Na^+$): 424.1189. Found: 424.1190.



Compound SI-39: To a stirred solution of **SI-38** (297 mg, 0.774 mmol), **SI-34** (230 mg, 0.774 mmol) and PPh_3 (175 mg, 0.774 mmol) in THF (3.9 mL) at 0 °C was added diethyl azodicarboxylate (DEAD, 2.2 M solution in toluene, 0.35 mL, 0.774 mmol), and the resulting mixture was stirred at room temperature for 1 h. After evaporation, the crude mixture was filtered through a short pad of silica gel (Hexane/AcOEt = 2/1) and the obtained residue was purified by flash column chromatography (SiO_2, $CHCl_3$/AcOEt = 50/1) to give **SI-13** (241 mg, 58% yield) as white solid.; Mp 121–122 °C; IR (ATR) ν 1752, 1594, 1518, 1494, 1444, 1341, 1263, 1161, 1091, 954; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.78 (s, 3H), 4.08 (t, *J* = 2.0 Hz, 2H), 4.39 (t, *J* = 2.0 Hz, 2H), 4.48 (s, 2H), 5.21 (s, 2H), 6.97 (d, *J* = 9.2 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.36–7.41 (m, 5H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.15 (dd, *J* =

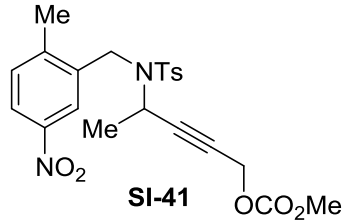
2.4 Hz, 8.4 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 37.5, 45.1, 55.1, 55.1, 70.9, 79.4, 80.4, 111.5, 125.4, 125.5, 125.7, 127.3 (2C), 127.8 (2C), 128.5, 128.8 (2C), 129.6 (2C), 135.3, 135.6, 141.5, 144.0, 155.7, 161.4; (+)-ESI-HRMS. Calcd for $C_{27}H_{26}N_2NaO_8S^+$ ($M+Na^+$): 561.1302. Found: 561.1318.

Reference for Compound **SI-38**: *J. Org. Chem.* **1995**, *60*, 601.



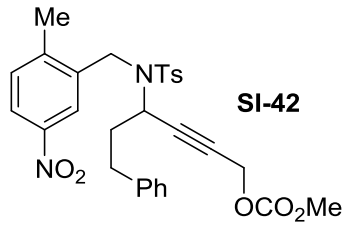
SI-40

SI-40 was prepared from **SI-38** and **SI-35** according to the general procedure. White solid; Mp 82–83 °C; IR (ATR) ν 1753, 1593, 1518, 1444, 1340, 1258, 1142, 1093, 954, 897, 832 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 9H), 1.08–1.13 (m, 2H), 3.03–3.07 (m, 2H), 3.78 (s, 3H), 4.08 (t, J = 1.6 Hz, 2H), 4.63 (s, 2H), 4.67 (t, J = 1.6 Hz, 2H), 5.24 (s, 2H), 7.01 (d, J = 8.8 Hz, 1H), 7.37–7.45 (m, 5H), 8.17 (dd, J = 2.8 Hz, 8.6 Hz, 1H), 8.32 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ –2.12, 9.94, 37.0, 45.1, 48.7, 55.1, 55.1, 71.0, 79.4, 81.6, 111.5, 125.2, 125.4, 125.9, 127.4 (2C), 128.5, 128.8 (2C), 135.2, 141.6, 155.0, 161.3; (+)-ESI-HRMS. Calcd for $C_{25}H_{32}N_2NaO_8SSi^+$ ($M+Na^+$): 571.1541. Found: 571.1537.



SI-41

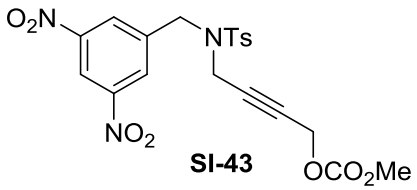
SI-41 was prepared from the corresponding benzyl alcohol derivative (*ACS Med. Chem. Lett*. **2014**, *5*, 527.) and **SI-36** according to the general procedure. White solid; Mp 118–119 °C; IR (ATR) ν 1751, 1520, 1444, 1343, 1260, 1157, 1089, 951, 918, 814; ^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 7.2 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.80 (s, 3H), 4.28 (d, J = 16.0 Hz, 1H), 4.46–4.57 (m, 2H), 4.59 (d, J = 16.0 Hz, 1H), 5.05 (q, J = 7.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 8.01 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.6, 21.5, 22.0, 46.0, 46.7, 55.1, 55.1, 79.7, 84.3, 122.3, 123.7, 127.6 (2C), 129.6 (2C), 131.0, 135.4, 137.4, 143.7, 144.0, 146.5, 155.0; (+)-ESI-HRMS. Calcd for $C_{22}H_{24}N_2NaO_7S^+$ ($M+Na^+$): 483.1196. Found: 483.1201.



SI-42

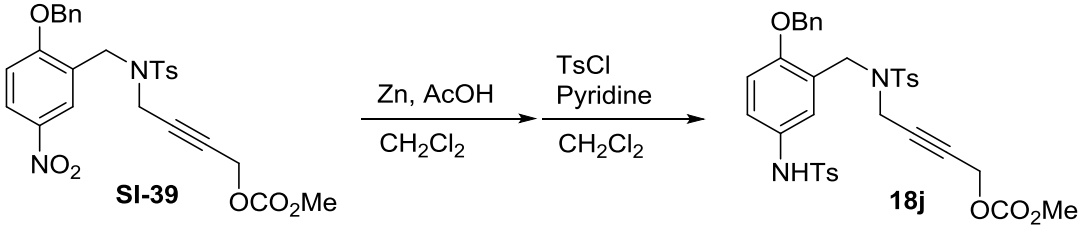
SI-42 was prepared from the corresponding benzyl alcohol derivative (*ACS Med. Chem. Lett*. **2014**, *5*, 527.) and

SI-37 according to the general procedure. White solid; Mp 108–109 °C; IR (ATR) ν 1753, 1521, 1444, 1344, 1262, 1162, 1091, 954, 814; ^{1}H NMR ($CDCl_3$): δ 1.59–1.70 (m, 2H), 2.44 (s, 3H), 2.50 (s, 3H), 2.55–2.68 (m, 2H), 3.80 (s, 3H), 4.31 (d, *J* = 16.0 Hz, 1H), 4.49–4.61 (m, 2H), 4.62 (d, *J* = 16.0 Hz, 1H), 4.80 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.14–7.31 (m, 6H), 7.66 (d, *J* = 8.4 Hz, 2H), 8.00 (dd, *J* = 2.4 Hz, 8.2 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 19.6, 21.5, 32.2, 36.7, 46.5, 51.1, 55.0, 55.1, 80.9, 83.2, 122.4, 124.1, 126.2, 127.6 (2C), 128.2 (2C), 128.4 (2C), 129.6 (2C), 131.1, 135.2, 137.0, 140.0, 144.0, 144.0, 146.4, 155.0; (+)-ESI-HRMS. Calcd for $C_{29}H_{30}N_2NaO_7S^+$ ($M+Na^+$): 573.1666. Found: 573.1655.



SI-43

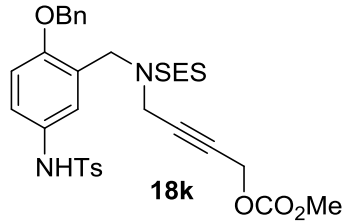
SI-43 was prepared from the corresponding benzyl alcohol derivative (commercially available) and **SI-34** according to the general procedure. White solid; Mp 108–109 °C; IR (ATR) ν 3099, 1750, 1597, 1443, 1091, 1017, 949, 923, 903, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 3.81 (s, 3H), 4.08 (t, *J* = 2.0 Hz, 2H), 4.46 (t, *J* = 2.0 Hz, 2H), 4.55 (s, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.57 (d, *J* = 2.4 Hz, 2H), 8.99 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.5, 37.5, 49.6, 54.8, 55.2, 79.3, 80.7, 118.5, 127.7 (2C), 128.4 (2C), 129.9 (2C), 134.8, 140.6, 144.6, 148.7 (2C), 155.0; (+)-ESI-HRMS. Calcd for $C_{20}H_{19}N_3NaO_9S^+$ ($M+Na^+$): 500.0734. Found: 500.0737.



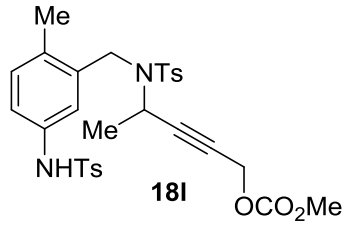
SI-39 **18j**

Compound 18j: To a solution of **SI-39** (222 mg, 0.412 mmol) and zinc powder (1.62 g, 24.7 mmol) in CH_2Cl_2 (5.2 mL) was added AcOH (0.62 mL) at 0 °C, and the mixture was stirred at room temperature. After 1 h, the reaction mixture was filtered through a short pad of celite, and the filtrate was added aq. $NaHCO_3$ and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a stirred solution of crude aniline (0.412 mmol), pyridine (37 μL, 0.453mmol) in CH_2Cl_2 (0.41 mL) at 0 °C was added TsCl (137 mg, 0.453 mmol) and the reaction was stirred at room temperature. After 1 h, the reaction mixture was concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **18j** (231 mg, 85% yield, 2 steps) as colorless oil.; IR (ATR) ν 1751, 1499, 1445, 1328, 1261, 1155, 1091, 951, 907, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.42 (s, 3H), 3.78 (t, *J* = 1.8 Hz, 2H), 3.81 (s, 3H), 4.28 (s, 2H), 4.35 (t, *J* = 1.8 Hz, 2H), 5.02 (s, 2H), 6.72 (br-s, 1H), 6.82 (d, *J* = 9.2 Hz, 1H), 6.91 (d, *J* = 2.8 Hz, 1H), 7.16–7.22 (m, 3H), 7.27–7.39 (m, 7H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.5, 36.6, 44.8, 55.1, 55.3,

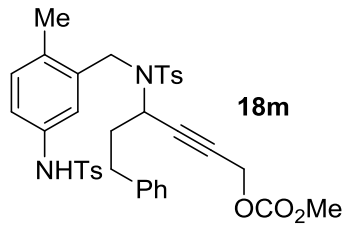
79.1, 80.6, 112.7, 124.4, 124.5, 125.3, 127.2 (2C), 127.3 (2C), 127.8 (2C), 128.0, 128.5 (2C), 129.4 (2C), 129.5, 129.5 (2C), 135.6, 135.9, 136.5, 143.6, 143.6, 143.7, 154.8, 155.2; (+)-ESI-HRMS. Calcd for $C_{34}H_{34}N_2NaO_8S_2^+$ ($M+Na^+$): 685.1649. Found: 685.1650.



Compound 18k: Colorless oil; IR (ATR) ν 1753, 1324, 1261, 1217, 1157, 1091, 896, 834 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.03 (s, 9H), 1.02–1.06 (m, 2H), 2.38 (s, 3H), 2.95–3.00 (m, 2H), 3.77 (t, *J* = 2.0 Hz, 2H), 3.80 (s, 3H), 4.44 (s, 2H), 4.64 (t, *J* = 1.8 Hz, 2H), 5.06 (s, 2H), 6.66 (br-s, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 7.18–7.22 (m, 3H), 7.33–7.42 (m, 5H), 7.58 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ –2.1 (3C), 9.9, 21.5, 36.2, 44.9, 48.5, 55.2, 55.3, 70.4, 79.0, 81.8, 112.7, 124.5, 124.8, 124.9, 127.3 (2C), 127.3 (2C), 128.1, 128.6 (2C), 129.5 (2C), 129.6, 135.9, 136.4, 143.7, 154.7, 155.2; (+)-ESI-HRMS. Calcd for $C_{32}H_{40}N_2NaO_8S_2Si^+$ ($M+Na^+$): 695.1888. Found: 695.1883.

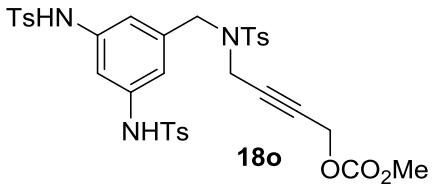


Compound 18l: Colorless amorphous; IR (ATR) ν 1752, 1263, 1155, 1091, 900, 748, 660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (d, *J* = 6.6 Hz, 3H), 2.29 (s, 3H), 2.34 (s, 3H), 2.44 (s, 3H), 3.85 (t, *J* = 2.0 Hz, 3H), 3.97 (d, *J* = 15.4 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 2H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.88 (q, *J* = 6.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.10–7.18 (m, 5H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.6, 21.4, 21.5, 21.8, 46.3, 46.8, 55.2, 55.3, 79.4, 84.3, 120.5, 122.4, 127.2 (2C), 127.6 (2C), 129.5 (2C), 129.5 (2C), 131.0, 133.3, 134.6, 135.2, 135.9, 136.0, 143.6, 143.7, 155.1; (+)-ESI-HRMS. Calcd for $C_{29}H_{32}N_2NaO_7S_2^+$ ($M+Na^+$): 607.1543. Found: 607.1549.

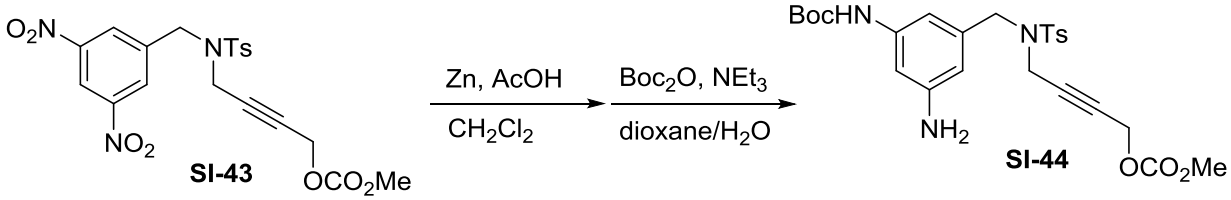


Compound 18m: Colorless amorphous; IR (ATR) ν 1749, 1263, 1157, 1091, 747, 700, 661 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44–1.31 (m, 2H), 2.22 (s, 3H), 2.38 (s, 3H), 2.43 (t, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 3.86 (s, 3H), 3.95 (d, *J* = 14.6 Hz, 1H), 4.55 (d, *J* = 0.8 Hz, 2H), 4.65 (d, *J* = 14.6 Hz, 1H), 4.69–4.73 (m, 1H), 6.83 (d, *J* = 6.4 Hz, 2H),

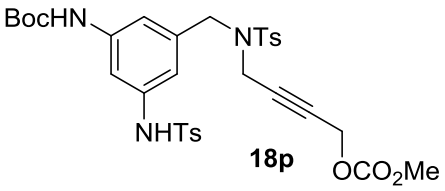
6.98 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 7.13–7.21 (m, 6H), 7.30 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 18.7, 21.4, 21.5, 32.3, 36.9, 47.5, 50.8, 55.3, 55.5, 80.7, 83.3, 120.5, 123.3, 125.6, 127.1 (2C), 127.6 (2C), 128.2 (2C), 128.3 (2C), 129.5 (2C), 129.5 (2C), 131.4, 134.0, 134.7, 135.0, 135.4, 136.0, 140.5, 143.5, 143.8, 155.2; (+)-ESI-HRMS. Calcd for $C_{36}H_{38}N_2NaO_7S_2^+$ ($M+Na^+$): 697.2013. Found: 697.2021.



Compound 18o: Colorless amorphous; IR (ATR) ν 3262, 1753, 1605, 1445, 1327, 1266, 1091, 1030, 954, 907, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 6H), 2.43 (s, 3H), 3.68 (t, J = 2.0 Hz, 2H), 3.83 (s. 3H), 4.08 (s, 2H), 4.43 (t, J = 2.0 Hz, 2H), 6.73 (d, J = 2.0 Hz, 2H), 7.06 (t, J = 2.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 4H), 7.31 (d, J = 8.0 Hz, 2H), 7.35 (br-s, 2H), 7.64 (d, J = 8.0 Hz, 4H), 7.70 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.5 (2C), 36.0, 49.6, 55.1, 55.4, 79.7, 79.8, 111.2, 116.3, 127.4 (4C), 127.7 (2C), 129.6 (2C), 129.7 (4C), 135.2, 135.6 (2C), 137.3, 138.3 (2C), 144.0 (2C), 144.0 (2C), 155.2; (+)-ESI-HRMS. Calcd for $C_{34}H_{35}N_3NaO_9S_3^+$ ($M+Na^+$): 748.1428. Found: 748.1441.

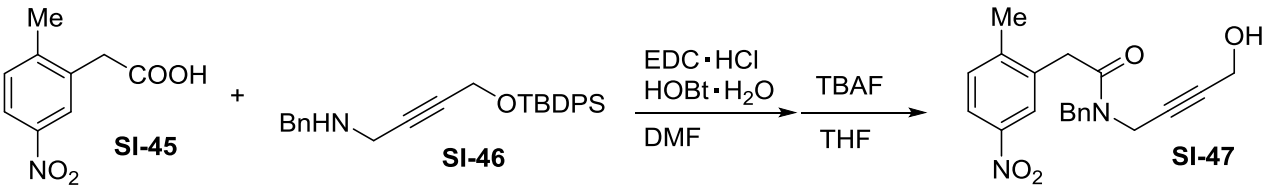


SI-44: To a solution of **SI-43** (955 mg, 2.00 mmol) and zinc powder (1.96 g, 30.0 mmol) in CH_2Cl_2 (25 mL) was added AcOH (3.0 mL) at 0 °C, and the mixture was stirred at room temperature. After 1 h, the reaction mixture was filtered through a short pad of celite, and the filtrate was added aq. $NaHCO_3$ and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a stirred solution of crude aniline (2.00 mmol), NEt_3 (0.31 mL, 2.20 mmol) in dioxane (6.67 mL) and water (3.33 mL) at 0 °C was added Boc_2O (437 mg, 2.00 mmol) and the reaction was stirred at room temperature. After 16 h, the reaction was quenched with HCl aq. and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **SI-44** (284 mg, 27% yield, 2 steps) as white amorphous.; IR (ATR) ν 2980, 1720, 1608, 1535, 1368, 1346, 1018, 954, 875, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9H), 2.44 (s, 3H), 3.73 (br-s, 2H), 3.82 (s, 3H), 3.98 (t, J = 2.0 Hz, 2H), 4.15 (s, 2H), 4.44 (t, J = 2.0 Hz, 2H), 6.35 (t, J = 2.0 Hz, 1H), 6.45 (t, J = 2.0 Hz, 1H), 6.54 (br-s, 1H), 7.00 (br-s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 28.3 (3C), 35.9, 50.0, 55.1, 55.2, 79.3, 80.2, 80.4, 104.5, 108.8, 109.7, 127.8 (2C), 129.4 (2C), 135.7, 136.5, 139.7, 143.6, 147.7, 152.6, 155.1; (+)-ESI-HRMS. Calcd for $C_{25}H_{31}N_3NaO_7S^+$ ($M+Na^+$): 540.1775. Found: 540.1764.



Compound 18p: Colorless amorphous; IR (ATR) ν 3268, 2980, 1729, 1607, 1540, 1495, 1444, 1367, 1329, 1018, 950, 904, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 2.36 (s, 3H), 2.44 (s, 3H), 3.82 (t, *J* = 2.0 Hz, 2H), 3.83 (s, 3H), 4.16 (s, 2H), 4.45 (t, *J* = 2.0 Hz, 2H), 6.75 (s, 2H), 6.75 (br-s, 1H), 7.07 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.5, 28.2 (3C), 36.0, 49.8, 55.1, 55.3, 79.6, 79.8, 80.8, 110.0, 114.7, 114.7, 127.3 (2C), 127.8 (2C), 129.5 (2C), 129.6 (2C), 135.3, 135.7, 136.8, 137.8, 139.8, 143.8, 134.9, 152.4, 155.1; (+)-ESI-HRMS. Calcd for $C_{32}H_{37}N_3NaO_9S_2^+$ ($M+Na^+$): 694.1863. Found: 694.1872.

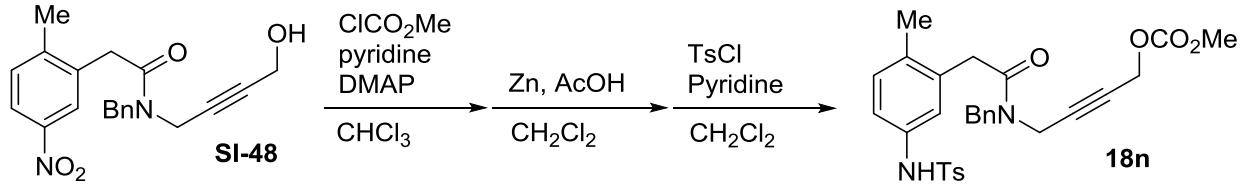
2-4-3. Synthesis of 18n.



Compound SI-47: To a stirred solution of **SI-45** (195 mg, 1.00 mmol), **SI-46** (414 mg, 1.00 mmol) and 1-hydroxybenzotriazole monohydrate (149 mg, 1.10 mmol) in DMF (5.0 mL) was added EDC hydrochloride (211 mg, 1.10 mmol), and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with water and the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the obtained crude residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 7/1) to give the amido compound. To a stirred solution of the amido compound (555 mg, 0.939 mmol) in DMF (4.7 mL) at 0 °C was added TBAF (1.13 mL, 1M solution in THF, 0.73 mmol). After being stirred for 1 h at room temperature, the reaction mixture was diluted with AcOEt. The obtained mixture was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 1/1) to give **SI-47** (180 mg, 86% yield, 2 steps) as white solid.; Mp 104–105 °C; IR (ATR) ν 1643, 1517, 1441, 1345, 1214, 1127, 1026, 816; ^1H NMR (DMSO-d_6, 140 °C): δ 2.31 (s, 3H), 3.96 (s, 2H), 4.09 (s, 2H), 4.25 (s, 2H), 4.71 (s, 2H), 7.27–7.37 (m, 5H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (DMSO-d_6, 140 °C): δ 18.5, 35.9, 36.7, 48.5, 49.1, 78.5, 83.8, 120.7, 123.9, 126.5, 126.8, 127.8 (2C), 130.2 (2C), 136.0, 136.6, 144.9, 145.5, 168.9; (+)-ESI-HRMS. Calcd for $C_{20}H_{20}N_2NaO_4^+$ ($M+Na^+$): 375.1315. Found: 375.294.

Reference for Compound **SI-45**: *J. Chem. Soc., Perkin Trans. 1,* **2000**, 1601.

Reference for Compound **SI-46**: *Chem. Eur. J.* **2012**, *18*, 15578.



Compound 18n: To a stirred solution of **SI-48** (302 mg, 0.857 mmol) and DMAP (21 mg, 0.171 mmol) in $CHCl_3$ (1.4 mL) and pyridine (0.29 mL) at 0 °C was added methyl chloroformate (0.17 mL, 2.14 mmol), and the resulting mixture was kept stirring for 3 h at room temperature. The reaction was quenched with 1N HCl at 0 °C, and then the resulting mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a solution of crude sample (0.841 mmol) in CH_2Cl_2 (5.2 mL) was added Zinc powder (3.30 g, 50.4 mmol) at 0 °C, and the mixture was stirred at room temperature. After 1 h, the reaction mixture was filtered through a short pad of celite, and the obtained residue was added aq. $NaHCO_3$ and diluted with AcOEt. The organic layer was separated and then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained residue was used for the next reaction without further purification. To a stirred solution of crude aniline (0.841 mmol), pyridine (68 μL, 0.841mmol) in CH_2Cl_2 (0.84 mL) at 0 °C was added TsCl (255 mg, 0.841 mmol) and the reaction was stirred at room temperature. After 1 h, the reaction mixture was concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 2/1) to give **18n** (382 mg, 85% yield, 2 steps) as colorless oil.; IR (ATR) ν 1754, 1641, 1443, 1262, 1215, 1156, 747, 699, 664 cm^{-1}; ^1H NMR (DMSO-d_6, 140 °C): δ 2.08 (s, 3H), 2.33 (s, 3H), 3.67 (s, 2H), 3.75 (s, 3H), 4.20 (s, 2H), 4.63 (s, 2H), 4.73 (s, 2H), 6.87 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.25–7.35 (m, 7H), 7.63 (d, *J* = 8.4 Hz, 2H), 9.49 (br-s, 1H); ^{13}C NMR (DMSO-d_6, 140 °C): δ 17.5, 20.0, 35.7, 37.2, 49.2, 54.2, 54.7, 77.5, 82.4, 118.7, 122.1, 126.0 (2C), 126.5, 126.7 (2C), 127.7 (2C), 128.7 (2C), 129.6, 132.0, 134.3, 134.9, 136.5, 137.2, 142.1, 153.8, 169.4; (+)-ESI-HRMS. Calcd for $C_{29}H_{30}N_2NaO_6S^+$ ($M+Na^+$): 557.1717. Found: 557.1723.

2-5. Evaluation of Antiproliferative Activities against Cancer Cells and Normal Cells

AGS, MKN74, Huh7, WI38 and IMR90 cells were obtained from the JCRB. RKO cells were obtained from the ATCC. HL-60 cells were maintained in RPMI-1640 medium containing 100 U/mL penicillin, 100 μg/mL streptomycin, and 5% heat-inactivated fetal bovine serum (FBS). AGS and MKN74 cells were maintained in RPMI-1640 medium containing 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% heat-inactivated FBS. RKO cells were maintained in Eagle's minimum essential medium (MEM) containing 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% heat-inactivated FBS. WI38 and IMR90 cells were maintained in Eagle's MEM containing 100 U/mL penicillin, 100 μg/mL streptomycin, 100 μM non-essential amino acids and 10% heat-inactivated FBS. Huh7 cells were maintained in Dulbecco's modified Eagle's MEM containing 100 U/mL penicillin, 100 μg/mL streptomycin and 10% heat-inactivated FBS. Cells were grown in a humidified incubator at 37 °C under 5% CO_2/95% air.

In the case of HL-60 cells, antiproliferative activities of compounds were examined based on the cell viabilities determined by using alamarBlue assay. HL-60 cells (3×10^4 cells/mL) were suspended in fresh medium in a 96-well plate (100 μL/well) and treated with test compounds (DMSO solution, final DMSO concentration: 0.5%). After 3 days, alamarBlue reagent (Invitrogen) was added to each well (10 μL/well). The cell viability was determined based on the increase of fluorescence (excitation 560 nm/emission 590 nm) during 1-2 h incubation measured with SpectraMax M5 microplate reader (Molecular Devices). Data are presented as mean ± S.D. (n = 4). The dose-response curves and IC_{50} values were calculated by Origin 9.0 software.

In the cases of RKO, AGS, MKN74, Huh7, WI38 and IMR90 cells, cells were plated at 2000 cells/well in each wells on 96-well plates with 50 μL of culture medium. One day later, the medium was changed to 100 μL of fresh medium containing various concentrations of the compounds. In all experiments, the final DMSO concentration was the same (0.1%). After treatment with the compounds for 72 h, 10 μL of WST-8 reagent (Dojindo) was added into each well followed by incubation for 2 h at 37 °C. Absorbance was then measured at 450 nm using SpectraMax PLUS 384 microplate reader (Molecular Devices). The absorbance of the control well (C), the treated wells (T) and the treated wells at time 0 (T0) were measured. The growth IC_{50} was calculated as $100 \times [(T - T0)/(C - T0)] = 50$.

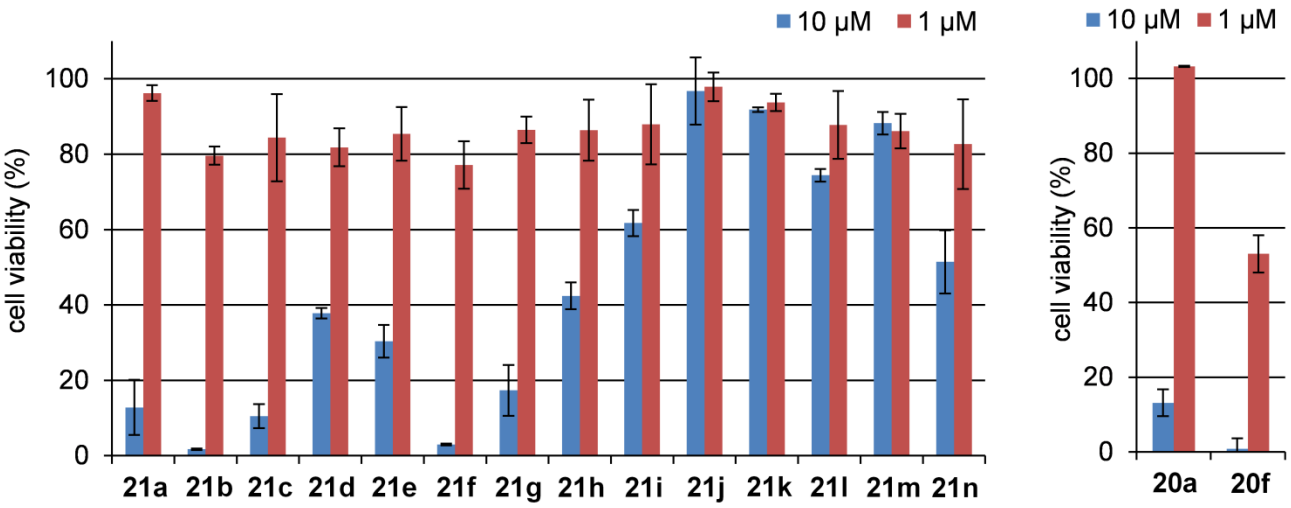


Figure S1. Antiproliferative activities of compounds in HL-60 cells.

HL-60 cells were treated with 1 or 10 μM of the compound (final DMSO concentration: 0.5%). After 3 days, cell viability was determined by alamarBlue assay with DMSO-treated control as 100%. Red and blue blocks indicate cell viability at 1.0 and 10 μM Data are presented as mean ± S.D. (n = 4).

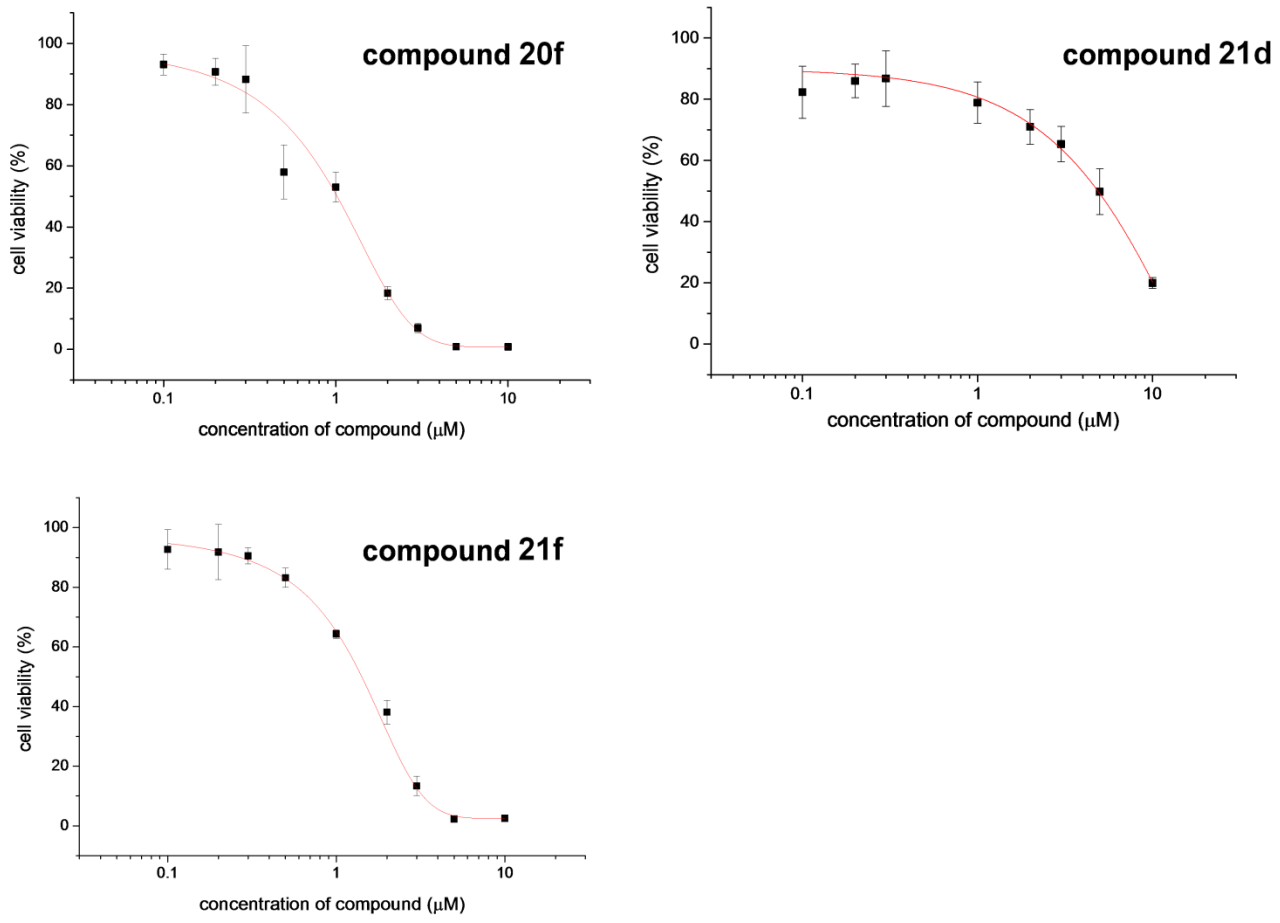


Figure S2 Dose-response curves of compounds **20f**, **21d**, and **21f** in HL-60 cells.

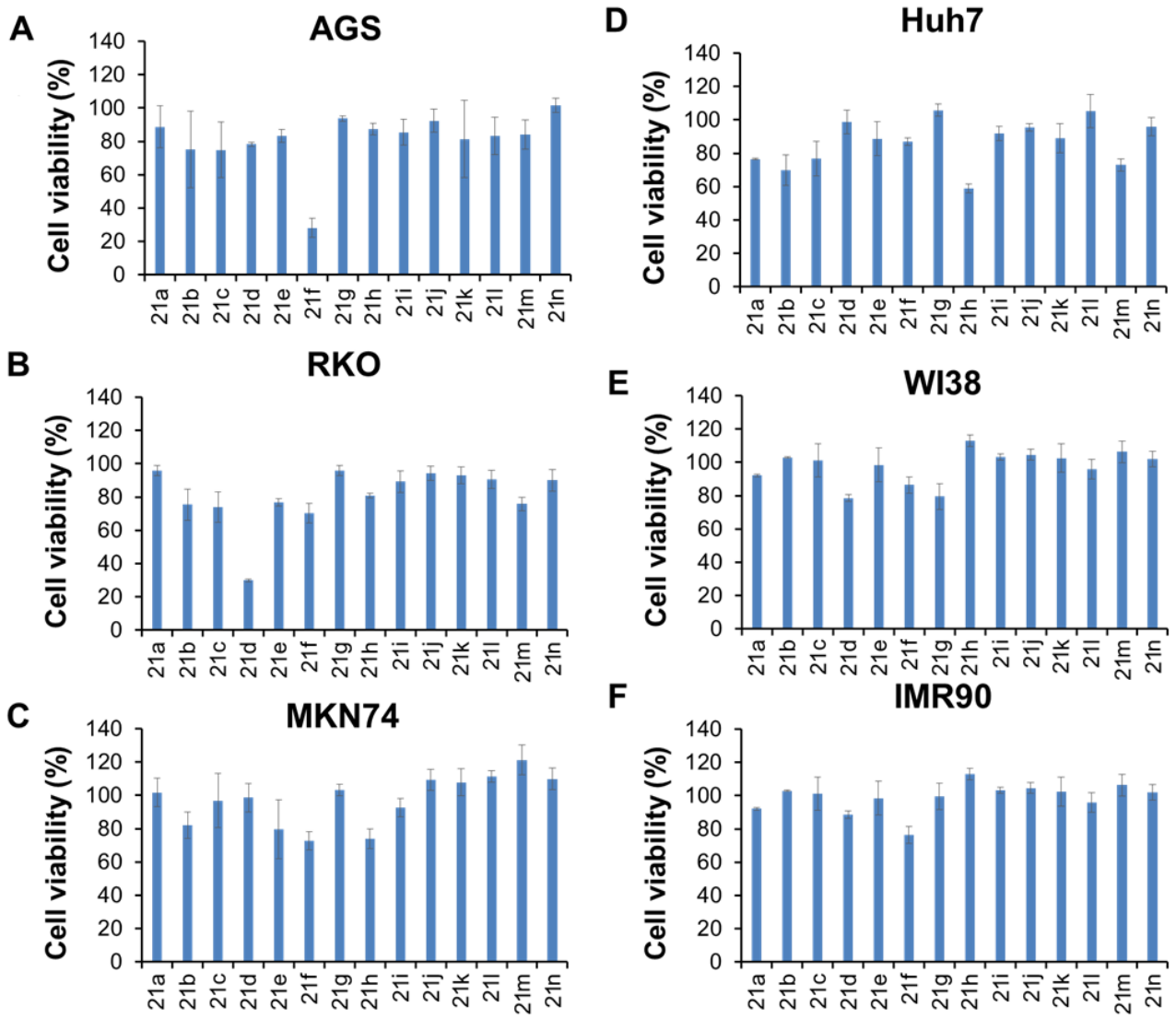


Figure S3. Antiproliferative activities of compounds in AGS, RKO, MKN, Huh7, WI38, and IMR90 cells.

AGS (A), RKO (B), MKN74 (C), Huh7 (D), WI38 (E) and IMR90 (F) cells were treated with 10 μM of the compound (final DMSO concentration: 0.1%) for 72 h. After treatment, cell viability was determined by colorimetric assay using WST-8 and estimated by comparison with DMSO-treated control as 100%. Error bars, standard deviation of the means of triplicate samples.

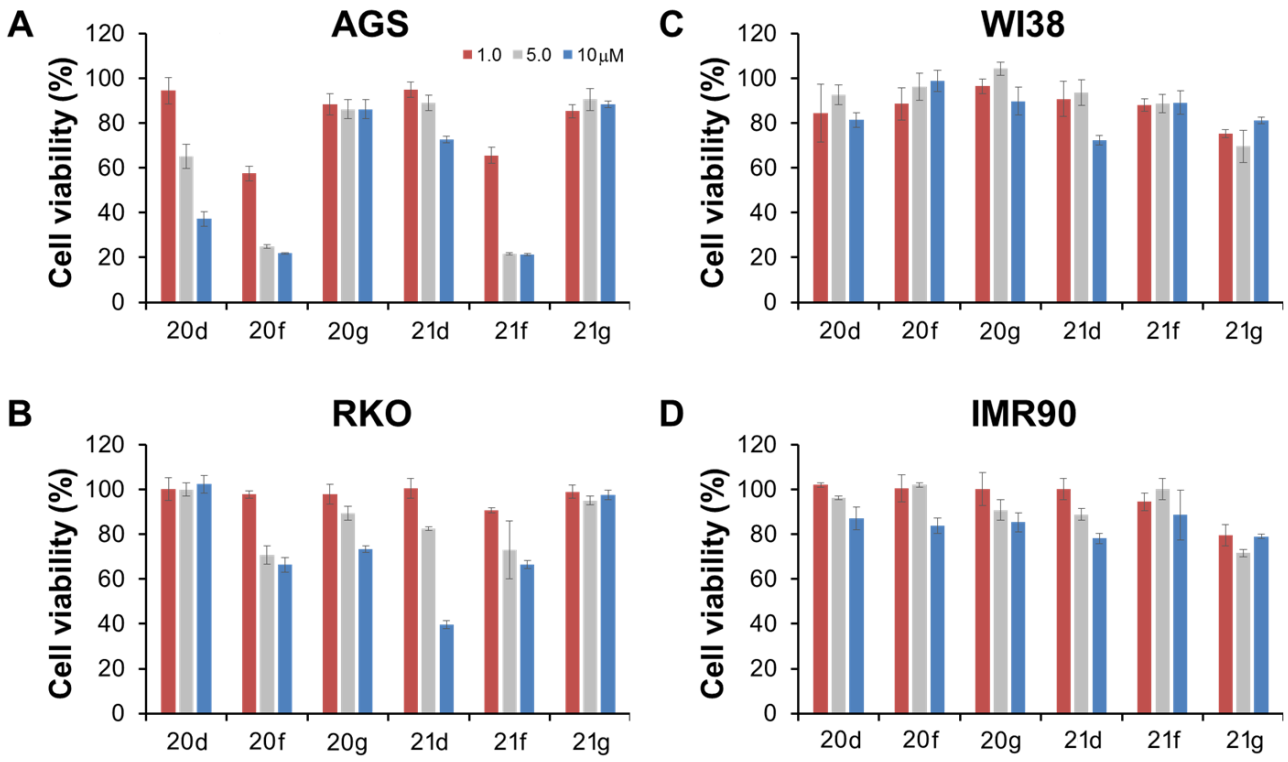
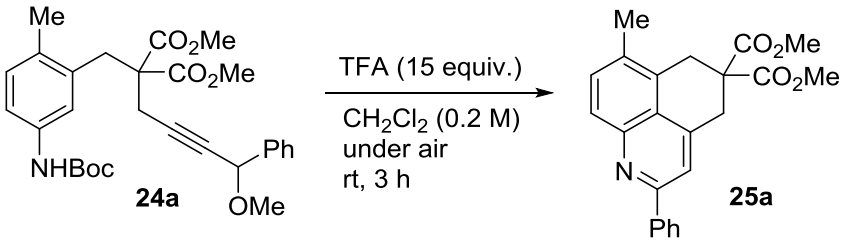


Figure S4. Dose-dependent antiproliferative activities of compounds in AGS, RKO, MKN, Huh7, WI38, and IMR90 cells.

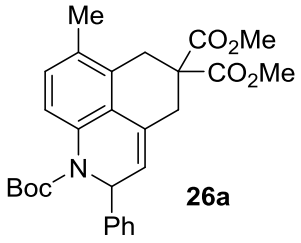
AGS (A), RKO (B), WI38 (C) and IMR90 (D) cells were treated with three doses of the compounds (final DMSO concentration: 0.1%). After treatment, cell viability was determined by colorimetric assay using WST-8 and estimated by comparison with DMSO-treated control as 100%. Red, gray and blue blocks indicate cell viability at 1.0, 5.0 and 10 μM, respectively. Error bars, standard deviation of the means of triplicate samples.

3. Syntehsis of 4,5-fused tricyclic quinolines.

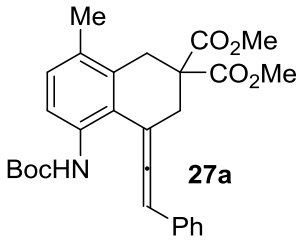
3-1. General Procedure for the Synthesis of 4,5-Fused Quinoline Derivatives and Product Characterizations



Compound 25a: To a stirred solution of **24a** (48.5 mg, 0.0952 mmol) in CH_2Cl_2 (1.90 mL) at room tenperature was added trifluoroacetic acid (0.106 mL, 1.43 mmol), and the resulting solution was stirred under air at the same temperature. After 3 h, the reaction was quenched with sat. aq. $NaHCO_3$ at 0 °C and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **25a** (27.5 mg, 77% yield) as white solid.; Mp 144 °C; IR (ATR) ν 1732, 1600, 1435, 1245, 1197, 1094, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.56 (s, 2H), 3.65 (s, 2H), 3.68 (s, 6H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.49–7.54 (m, 3H), 7.66 (s, 7.66), 7.92 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.8, 35.5, 53.0 (2C), 53.9, 117.3, 123.0, 127.4 (2C), 127.5, 128.7 (2C), 128.8, 129.1, 132.5, 132.9, 139.7, 141.9, 146.7, 156.2, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{22}NO_4^+$ 376.1543 ($M+H^+$) found 376.1540.

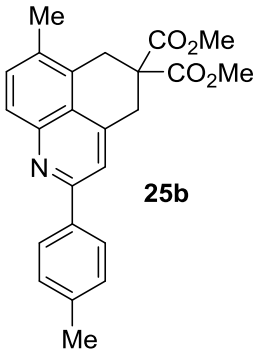


Compound 26a: Colorless oil; IR (ATR) ν 1735, 1690, 1477, 1320, 1250, 1161, 1070, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 2.24 (s, 3H), 2.91 (d, *J* = 16.8 Hz, 1H), 2.94–3.00 (m, 1H), 3.14 (dd, *J* = 2.0 Hz, 14.0 Hz, 1H), 3.53 (dd, *J* = 2.0 Hz, 16.8 Hz, 1H), 3.54 (s, 3H), 3.80 (s, 3H), 5.97 (dd, *J* = 2.0 Hz, 6.0 Hz, 1H), 6.02 (d, *J* = 6.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 7.13–7.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 28.4 (3C), 32.6, 35.1, 52.7, 53.0, 54.3, 81.4, 122.5, 123.3, 125.0, 125.0, 127.2, 127.6 (2C), 128.3, 128.4 (2C), 129.1, 130.1, 131.2, 132.4, 140.1, 153.4, 170.6, 171.1; (+)-ESI-HRMS. Calcd for $C_{28}H_{31}NNaO_6^+$ 500.2044 ($M+Na^+$) found 500.2032.



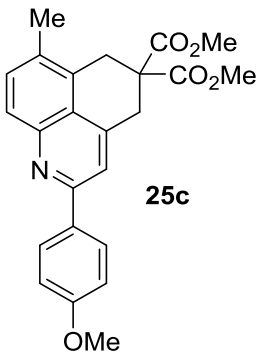
27a

Compound 27a: Colorless oil; IR (ATR) ν 1728, 1512, 1440, 1366, 1235, 1153, 1065, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.26 (s, 3H), 3.11 (d, *J* = 2.4 Hz, 2H), 3.18 (d, *J* = 16.8 Hz, 1H), 3.27 (d, *J* = 16.8 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 6.51 (t, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.22–7.36 (m, 5H), 7.50 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 27.9 (3C), 33.0, 35.8, 52.9, 53.0, 53.7, 79.7, 96.9, 100.2, 119.5, 127.3 (2C), 127.6, 128.3, 128.8 (2C), 129.7, 131.3, 132.5, 133.7, 134.4, 153.0, 170.9, 171.1, 204.4; (+)-ESI-HRMS. Calcd for $C_{28}H_{31}NNaO_6^+$ 500.2044 ($M+Na^+$) found 500.2027.



25b

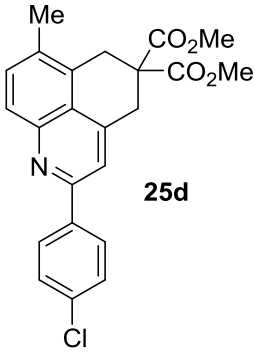
Compound 25b: White solid; Mp 138 °C; IR (ATR) ν 1733, 1601, 1556, 1436, 1245, 1197, 1092, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.49 (s, 3H), 3.56 (s, 2H), 3.64 (s, 2H), 3.68 (s, 6H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 21.3, 32.8, 35.5, 53.0 (2C), 54.0, 117.1, 122.9, 127.3 (2C), 127.4, 128.8, 129.5 (2C), 132.3, 132.8, 136.8, 139.1, 141.8, 146.7, 156.2, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{24}NO_4^+$ 390.1700 ($M+H^+$) found 390.1717.



25c

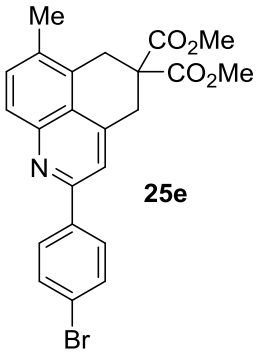
Compound 25c: White solid; Mp 153–154 °C; IR (ATR) ν 1736, 1603, 1557, 1517, 1437, 1253, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.55 (s, 2H), 3.66 (s, 2H), 3.68 (s, 6H), 3.88 (s, 3H), 7.00–7.05 (m, 2H),

7.51(d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.08–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.8, 35.5, 53.0 (2C), 54.0, 55.4, 114.1, 116.8, 122.7, 127.2, 128.8, 128.8, 132.1, 132.2, 132.9, 141.8, 146.7, 155.7, 160.6, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{24}NO_5^+$ 406.1649 ($M+H^+$) found 406.1671.



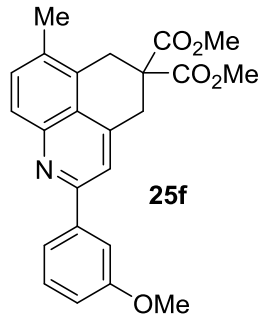
25d

Compound 25d: White solid; Mp 157 °C; IR (ATR) ν 1734, 1600, 1490, 1436, 1255, 1092, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.57 (s, 2H), 3.65 (s, 2H), 3.68 (s, 6H), 7.47 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.63 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 32.8, 35.5, 53.1 (2C), 53.9, 116.8, 123.0, 127.5, 128.7 (2C), 128.8, 128.9, 132.8, 133.1, 135.3, 138.1, 142.3, 146.7, 154.9, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{21}ClNO_4^+$ 410.1154 ($M+H^+$) found 410.1124.



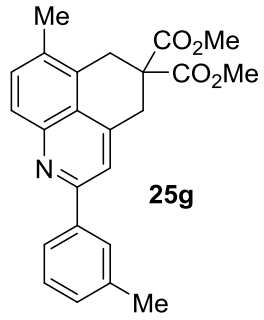
25e

Compound 25e: White solid; Mp 149–150 °C; IR (ATR) ν 1736, 1603, 1557, 1517, 1437, 1253, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.57 (s, 2H), 3.65 (s, 2H), 3.68 (s, 6H), 3.88 (s, 3H), 7.54 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.62–7.65 (m, 2H), 7.90 (d, J = 8.4 Hz, 1H), 8.01–8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 32.8, 35.5, 53.1 (2C), 53.9, 116.8, 123.1, 123.7, 127.5, 128.9, 129.0 (2C), 131.9 (2C), 132.9, 133.2, 138.5, 142.3, 146.7, 154.9, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{21}BrNO_4^+$ 454.0648 ($M+H^+$) found 454.0642.



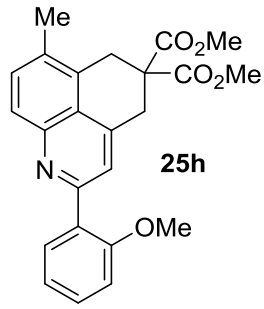
25f

Compound 25f: White solid; Mp 139–140 °C; IR (ATR) ν 1733, 1599, 1434, 1243, 1200, 1177, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.57 (s, 2H), 3.65 (s, 2H), 3.68 (s, 6H), 3.93 (s, 3H), 7.00 (dd, *J* = 2.4 Hz, 8.0 Hz, 1H), 7.41 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 32.8, 35.5, 53.1 (2C), 54.0, 55.4, 112.5, 115.3, 117.4, 119.9, 123.1, 127.5, 128.8, 129.7, 132.6, 133.0, 141.2, 142.0, 146.6, 156.0, 160.1, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{24}NO_5^+$ 406.1649 ($M+H^+$) found 406.1647.



25g

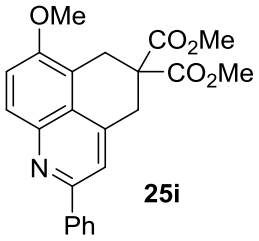
Compound 25g: White solid; Mp 177–178 °C; IR (ATR) ν 1734, 1600, 1559, 1436, 1312, 1255, 1199 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.49 (s, 3H), 3.56 (s, 2H), 3.65 (s, 2H), 3.68 (s, 6H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 21.6, 32.8, 35.5, 53.0 (2C), 54.0, 117.4, 123.0, 124.6, 127.4, 128.2, 128.6, 128.8, 129.9, 132.5, 132.9, 138.4, 139.6, 141.9, 146.7, 156.4, 170.9 (2C); (+)-ESI-HRMS. Calcd for $C_{24}H_{24}NO_4^+$ 390.1700 ($M+H^+$) found 390.1707.



25h

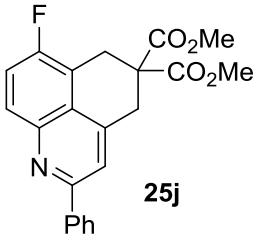
Compound 25h: White solid; Mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.56 (s, 2H), 3.64 (s, 2H), 3.68 (s, 6H), 3.85 (s, 3H), 7.01 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 7.10 (ddd, *J* = 0.8 Hz, 7.6 Hz, 8.0 Hz, 1H), 7.39 (ddd, *J* = 1.6 Hz, 7.6 Hz, 8.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.69 (s, 1H), 7.81 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.92

(d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 32.8, 35.4, 53.0 (2C), 53.9, 55.7, 111.4, 121.2, 121.6, 122.8, 127.4, 128.7, 129.7, 130.1, 131.5, 132.3, 132.5, 140.2, 146.7, 155.8, 157.7, 171.0 (2C); IR (ATR) ν 1734, 1600, 1493, 1436, 1239, 1055, 1024 cm^{-1}; (+)-ESI-HRMS. Calcd for $C_{24}H_{24}NO_5^+$ 406.1649 (M+H$^+$) found 406.1653.



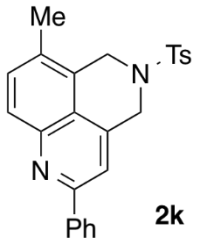
25i

Compound 25i: White solid; Mp 130 °C; IR (ATR) ν 1733, 1557, 1494, 1442, 1255, 1101, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 2H), 3.63 (s, 2H), 3.68 (s, 6H), 4.00 (s, 3H), 7.43–7.53 (m, 4H), 7.65 (s, 1H), 8.03 (d, J = 9.2 Hz, 1H), 8.10–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 35.4, 53.0 (2C), 53.4, 56.4, 116.5, 116.5, 117.5, 123.7, 127.3 (2C), 128.7 (2C), 128.9, 129.0, 139.8, 141.5, 143.1, 153.2, 155.2, 171.0 (2C); (+)-ESI-HRMS. Calcd for $C_{23}H_{22}NO_5^+$ 392.1492 (M+H$^+$) found 392.1480.



25j

Compound 25j: White solid; Mp 126 °C; IR (ATR) ν 1737, 1561, 1443, 1370, 1255, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 2H), 3.66 (s, 2H), 3.70 (s, 6H), 7.44–7.56 (m, 4H), 7.72 (s, 1H), 7.99–8.03 (m, 1H), 8.11–8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (d, J = 2.8 Hz), 35.2, 53.2 (2C), 115.5 (d, J = 18.2 Hz), 117.9, 119.7 (d, J = 25.7 Hz), 123.6 (d, J = 7.6 Hz), 127.4 (2C), 128.8 (2C), 129.3, 129.7 (d, J = 8.6 Hz), 139.4, 142.1, 143.5 (d, J = 265.0 Hz), 153.3, 156.6, 157.8, 170.5 (2C); (+)-ESI-HRMS. Calcd for $C_{22}H_{19}FNO_4^+$ 380.1293 (M+H$^+$) found 380.1305.

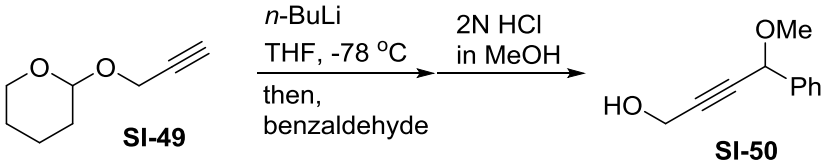


2k

Compound 25k: White solid; Mp 152 °C; IR (ATR) ν 1605, 1451, 1383, 1342, 1319, 1165, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.43 (s, 3H), 4.67 (s, 2H), 4.70 (s, 2H), 7.03 (d, J = 8.0 Hz, 2H), 7.46–7.56 (m,

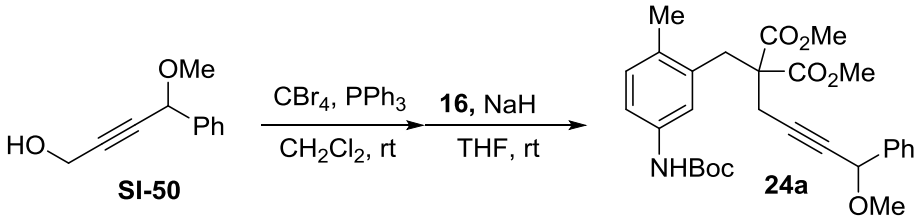
7H), 7.86 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 21.3, 46.5, 48.0, 115.0, 121.5, 126.4, 127.4 (2C), 127.4 (2C), 127.8, 128.9 (2C), 129.2 (2C), 129.4, 131.0, 132.7, 133.5, 139.0, 139.4, 143.8, 146.3, 156.3; (+)-ESI-HRMS. Calcd for $C_{25}H_{23}N_2O_2S^+$ 415.1475 ($M+Na^+$) found 415.1465.

3-2. General Procedures for the Synthesis of Substrates and Product Characterizations



Compound SI-50: To a stirred solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**SI-49:** 1.40 g, 10.0 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi (6.5 mL, 1.56 M solution in hexane, 10.0 mmol) dropwise, and the reaction mixture was stirred at the same temperature. After 30 min, benzaldehyde (1.0 mL, 10.0 mmol) was added to the reaction. After being stirred for 2 h at –78 °C, the reaction was quenched with sat. aq. NH_4Cl, and diluted with AcOEt. The mixture was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained mixture was passed through a short pad of silica to remove less polar compounds (eluting with hexane/AcOEt = 1/1), affording the corresponding propargyl alcohol derivative as an almost pure compound.

The propargyl alcohol was dissolved in 2N HCl/MeOH (12mL, 24.0 mmol) and the resulting mixture was stirred for 16 h at 40 °C. After concentration in vacuo, the obtained residue was purified by flash column chromatography (hexane/AcOEt = 5/1) to give **SI-50** (756 mg, 43% yield over 2 steps) as yellow oil. IR (ATR) ν 3398, 1452, 1280, 1187, 1119, 1070, 1016 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H), 4.36 (d, J = 2.0 Hz, 2H), 5.11 (t, J = 2.0 Hz, 1H), 7.31–7.40 (m, 3H), 7.47–7.50 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 51.1, 56.0, 127.3 (2C), 127.5, 128.5 (2C), 138.1; (–)-ESI-HRMS. Calcd for $C_{11}H_{11}O_2^-$ 175.0765 ($[M-H]^-$) found 175.0778.

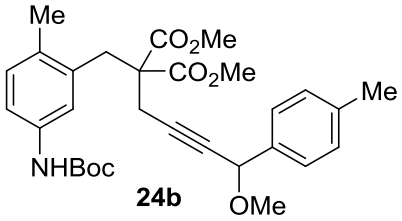


Compound 24a: To a stirred solution of **SI-50** (257 mg, 1.46 mmol) and PPh_3 (766 mg, 2.92 mmol) in CH_2Cl_2 (4.7 mL) at 0 °C was added carbon tetrabromide (968 mg, 2.92 mmol), and the resulting mixture was kept stirring for 3 h at room temperature. After concentration *in vacuo*, the obtained mixture was passed through a short pad of silica to remove triphenylphosphine oxide (eluting with hexane/AcOEt = 1/1). The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 100/1) to give the corresponding propargyl bromide derivative.

To a stirred solution of **16** (120 mg, 0.34 mmol) in THF (1.7 mL) at 0 °C was added NaH (20 mg, 0.51 mmol), and the reaction mixture was stirred at the same temperature. After 15 min, propargyl bromide (122 mg, 0.51 mmol) was added to the reaction. After being stirred for 4 h at room temperature, the reaction was quenched with sat. aq. NH_4Cl, and diluted with AcOEt. The resulting mixture was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 7/1) to give **24a** (144 mg, 83% yield) as colorless oil. IR (ATR) ν 1724, 1524, 1283, 1231, 1157, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.21 (s, 3H), 2.81 (d, J = 1.2 Hz, 2H), 3.41 (s, 3H), 3.43 (s, 2H), 3.73 (s, 6H), 5.10 (t, J = 1.2 Hz, 1H), 6.29 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 7.15 (dd, J = 5.6 Hz, 8.4 Hz, 1H), 7.32–7.40 (m, 3H), 7.48–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 23.0, 28.3 (3C), 34.2,

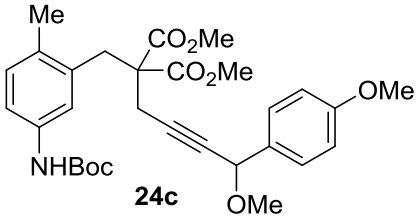
52.8 (2C), 55.8, 58.4, 73.0, 80.2, 81.6, 83.6, 117.4, 120.2, 127.3 (2C), 128.4, 128.4 (2C), 131.1, 131.9, 134.3, 136.1, 138.7, 152.6, 170.5 (2C); (+)-ESI-HRMS. Calcd for $C_{29}H_{35}NNaO_7^+$ 532.2306 ($M+Na^+$) found 546.2318.

Other substrates were also prepared according to the experimental procedures described above.



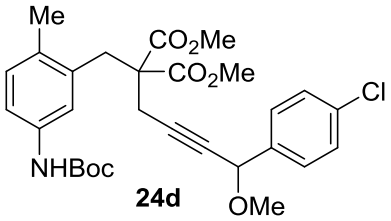
24b

Compound 24b: Amorphous; IR (ATR) ν 1724, 1522, 1283, 1231, 1156, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.21 (s, 3H), 2.35 (s, 3H), 2.81 (d, *J* = 1.2 Hz, 2H), 3.40 (s, 3H), 3.42 (s, 2H), 3.72 (s, 6H), 5.06 (t, *J* = 1.2 Hz, 1H), 6.30 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 7.15–7.19 (m, 3H), 7.37 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.2, 23.1, 28.3 (3C), 34.2, 52.8 (2C), 55.6, 58.4, 72.9, 80.2, 81.7, 83.4, 117.4, 120.2, 127.3 (2C), 129.1 (2C), 131.1, 132.0, 134.4, 135.7, 136.1, 138.1, 152.6, 170.5 (2C); (+)-ESI-HRMS. Calcd for $C_{30}H_{37}NNaO_7^+$ 546.2462 ($M+Na^+$) found 546.2449.



24c

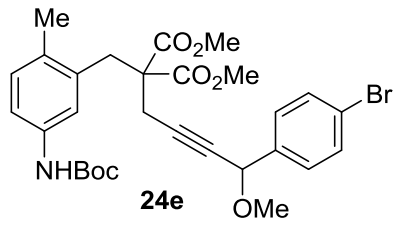
Compound 24c: Pale yellow oil; IR (ATR) ν 1726, 1510, 1366, 1284, 1243, 1157, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.22 (s, 3H), 2.82 (d, *J* = 2.0 Hz, 2H), 3.39 (s, 3H), 3.42 (s, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 5.05 (t, *J* = 2.0 Hz, 1H), 6.38 (s, 1H), 6.88–6.92 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.12–7.15 (m, 2H), 7.40–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 23.0, 28.3 (3C), 34.2, 52.8 (2C), 55.3, 55.5, 58.4, 72.6, 80.2, 81.7, 83.3, 113.7 (2C), 117.3, 120.2, 128.8 (2C), 130.8, 131.0, 131.9, 134.3, 136.1, 152.6, 159.6, 170.5 (2C); (+)-ESI-HRMS. Calcd for $C_{30}H_{37}NNaO_8^+$ 562.2411 ($M+Na^+$) found 562.2409.



24d

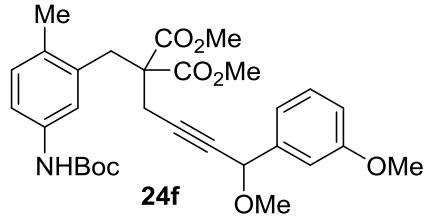
Compound 24d: White solid; Mp 105–106 °C; IR (ATR) ν 1724, 1521, 1284, 1231, 1158, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.21 (s, 3H), 2.82 (d, *J* = 1.6 Hz, 2H), 3.41 (s, 2H), 3.42 (s, 3H), 3.73 (s, 6H), 5.07 (t, *J* = 1.6 Hz, 1H), 6.32 (s, 1H), 7.03–7.14 (m, 3H), 7.34–7.36 (m, 2H), 7.42–7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 23.0, 28.3 (3C), 34.2, 52.8 (2C), 55.8, 58.4, 72.3, 80.3, 81.0, 84.0, 117.4, 120.2, 128.6 (2C),

128.7 (2C), 131.1, 131.9, 134.2, 134.3, 136.1, 137.2, 152.5, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{29}H_{34}ClNNaO_7^+$ 566.1916 ($M+Na^+$) found 566.1917.



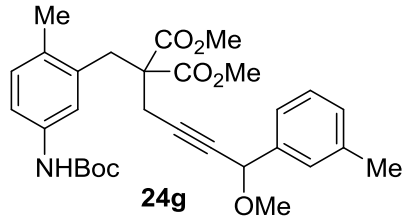
24e

Compound 24e: Pale yellow oil; IR (ATR) ν 1732, 1520, 1286, 1228, 1158, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.21 (s, 3H), 2.82 (d, *J* = 2.0 Hz, 2H), 3.41 (s, 2H), 3.42 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 5.06 (t, *J* = 2.0 Hz, 1H), 6.42 (s, 1H), 7.01–7.10 (m, 2H), 7.17 (s, 1H), 7.36–7.38 (m, 2H), 7.48–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 23.0, 28.3 (3C), 34.2, 52.8 (2C), 55.7, 58.3, 72.2, 80.1, 80.9, 84.0, 117.4, 120.1, 122.3, 128.9 (2C), 131.0, 131.5 (2C), 131.8, 134.2, 136.1, 137.7, 152.5, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{29}H_{34}BrNNaO_7^+$ 610.1411 ($M+Na^+$) found 610.1386.



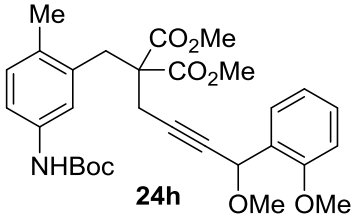
24f

Compound 24f: Pale yellow oil; IR (ATR) ν 1724, 1591, 1523, 1435, 1283, 1231, 1156, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.21 (s, 3H), 2.81 (d, *J* = 1.6 Hz, 2H), 3.42 (s, 2H), 3.42 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 3.83 (s, 3H), 5.07 (t, *J* = 1.6 Hz, 1H), 6.42 (s, 1H), 6.84–6.88 (m, 1H), 7.01–7.16 (m, 4H), 7.28–7.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 22.9, 28.3 (2C), 34.2, 52.8 (2C), 55.2, 55.7, 58.4, 72.9, 80.1, 81.4, 83.5, 112.5, 114.1, 117.4, 119.6, 120.2, 129.4, 131.0, 131.9, 134.3, 136.1, 140.1, 152.6, 159.7, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{30}H_{37}NNaO_8^+$ 562.2411 ($M+Na^+$) found 562.2402.



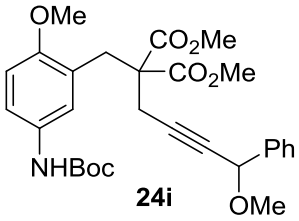
24g

Compound 24g: Colorless oil; IR (ATR) ν 1725, 1523, 1284, 1231, 1156, 1119, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.22 (s, 3H), 2.37 (s, 3H), 2.81 (d, *J* = 2.0 Hz, 2H), 3.42 (s, 2H), 3.42 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 5.06 (t, *J* = 2.0 Hz, 1H), 6.35 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.09–7.16 (m, 3H), 7.23–7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 21.3, 22.9, 28.2 (3C), 34.1, 52.7 (2C), 55.7, 58.3, 73.0, 80.1, 81.6, 83.4, 117.3, 120.1, 124.3, 127.9, 128.2, 129.0, 131.0, 131.8, 134.2, 136.1, 138.0, 138.5, 152.5, 170.4 (2C); (+)-ESI-HRMS. Calcd for $C_{30}H_{37}NNaO_7^+$ 546.2462 ($M+Na^+$) found 546.2470.



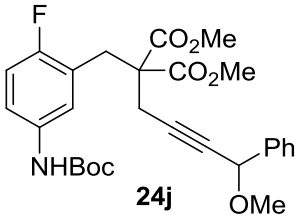
24h

Compound 24h: White solid; Mp 109–110 °C; IR (ATR) ν 1733, 1519, 1492, 1437, 1286, 1246, 1159, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.20 (s, 3H), 2.78 (d, *J* = 2.0 Hz, 2H), 3.40 (s, 2H), 3.44 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 5.48 (t, *J* = 2.0 Hz, 1H), 6.35 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.98–7.02 (m, 3H), 7.18–7.32 (m, 2H), 7.59–7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 22.9, 28.3(3C), 34.1, 52.7, 52.7, 55.6, 56.0, 58.3, 66.9, 80.1, 82.0, 82.2, 110.6, 117.3, 120.2, 120.5, 127.0, 128.2, 129.6, 131.0, 131.8, 134.3, 136.0, 152.6, 156.4, 170.4, 170.5; (+)-ESI-HRMS. Calcd for $C_{30}H_{37}NNaO_8^+$ 562.2411 ($M+Na^+$) found 562.2435.



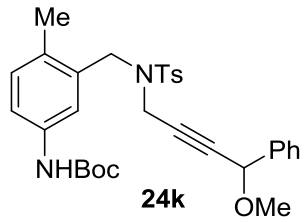
24i

Compound 24i: Amorphous; IR (ATR) ν 1719, 1507, 1211, 1157, 1126, 1065, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.73 (d, *J* = 2.0 Hz, 2H), 3.40 (s, 2H), 3.44 (s, 3H), 3.67 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 5.11 (t, *J* = 2.0 Hz, 1H), 6.15 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.31–7.42 (m, 4H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 28.3 (3C), 32.3, 52.6, 52.6, 55.5, 55.8, 57.5, 73.0, 80.0, 81.1, 83.8, 110.6, 119.0, 123.0, 124.2, 127.3 (2C), 128.3, 128.5 (2C), 131.1, 139.0, 152.9, 154.0, 170.5, 170.5; (+)-ESI-HRMS. Calcd for $C_{29}H_{35}NNaO_8^+$ 548.2255 ($M+Na^+$) found 548.2228.



24j

Compound 24j: Amorphous; IR (ATR) ν 1725, 1528, 1504, 1295, 1203, 1154, 1113, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.77 (d, *J* = 2.0 Hz, 2H), 3.40 (s, 2H), 3.44 (s, 3H), 3.74 (s, 6H), 5.12 (t, *J* = 2.0 Hz, 1H), 6.26 (s, 1H), 6.90 (dd, *J* = 8.8 Hz, 8.8 Hz, 1H), 7.01–7.04 (m, 1H), 7.32–7.42 (m, 4H), 7.51–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 28.3 (3C), 31.6, 52.9, 52.9, 55.8, 57.4, 73.0, 80.5, 81.7, 83.1, 115.5 (d, *J* = 23.8 Hz), 119.2, 122.3, 122.6 (d, *J* = 17.1 Hz), 127.3 (2C), 128.4, 128.5 (2C), 134.3, 138.9, 152.6, 157.3 (d, *J* = 241.2 Hz), 170.1, 170.1; (+)-ESI-HRMS. Calcd for $C_{28}H_{32}FNNaO_7^+$ 536.2055 ($M+Na^+$) found 536.2027.



24k

Compound 24k: Yellow oil; IR (ATR) ν 1722, 1520, 1347, 1231, 1156, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.28 (s, 3H), 2.38 (s, 3H), 3.23 (s, 3H), 3.96 (d, *J* = 18.4 Hz, 1H), 4.04 (d, *J* = 18.4 Hz, 1H), 4.24 (d, *J* = 17.6 Hz, 1H), 4.31 (d, *J* = 17.6 Hz, 1H), 4.78 (s, 1H), 6.30 (s, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.22–7.40 (m, 8H), 7.78 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.5, 28.3 (3C), 35.9, 48.4, 55.9, 72.8, 80.3, 80.3, 84.1, 118.4, 120.1, 127.1 (2C), 127.9 (2C), 128.5 (2C), 128.5, 129.6 (2C), 131.3, 132.3, 132.6, 135.4, 136.3, 138.3, 143.6, 152.7; (+)-ESI-HRMS. Calcd for $C_{31}H_{36}N_2NaO_5S^+$ 571.2237 ($M+Na^+$) found 571.2173.

主要論文目録

本学位論文内容は下記の発表論文による。

1. Yuta Suzuki, Tetsuhiro Nemoto, Kazumi Kakugawa, Akinari Hamajima, Yasumasa Hamada:
   “Asymmetric Synthesis of Chiral 9,10-Dihydrophenanthrenes Using Pd-Catalyzed Asymmetric Intramolecular Friedel–Crafts Allylic Alkylation of Phenols”
   Organic Letters (ACS), Volume 14, Issue 9, pp. 2350-2353, (2012)

2. Yuta Suzuki, Nobuaki Matsuo, Tetsuhiro Nemoto, Yasumasa Hamada:
   “Enantioselective total syntheses of cedrelin A and methylated paralycolin B using Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols”
   Tetrahedron (Elsevier), Volume 69, Issue 29, pp. 5913-5919, (2013)

3. Yuta Suzuki, Yuito Tanaka, Shun-ichi Nakano, Kosuke Dodo, Natsumi Yoda, Ken-ichi Shinohara, Kazuko Kita, Atsushi Kaneda, Mikiko Sodeoka, Yasumasa Hamada, Tetsuhiro Nemoto:
   “Platinum-Catalyzed Friedel–Crafts-type C–H Coupling–Allylic Amination Cascade to Synthesize 3,4-Fused Tricyclic Indoles”
   Chemistry-A Europian Journal (Wiley), *in press*

4. Yuta Suzuki, Tetsuhiro Nemoto, Shun-ichi Nakano, Zengduo Zhao, Yuta Yoshimatsu, Yasumasa Hamada:
   “Synthesis of 4,5-Fused Tricyclic Quinolines via an Acid-Promoted Intramolecular Friedel–Crafts Allenylation of Aniline Derivatives”
   Tetrahedron Letters (Elsevier), Volume 55, Issue 49, pp. 6726-6729, (2014).

謝辞

本研究を行うにあたり、終始御懇篤なる御指導、御鞭撻を賜りました濱田康正教授に深甚なる感謝の意を表します。

本研究を遂行するにあたり、多大なる御指導、御討論を賜りました根本哲宏教授に深く感謝致します。

本研究において有益な御指導、御助言を賜りました濱嶋祥就助教、原田慎吾助教に厚く御礼致します。

本研究に御協力頂いた趙増奪修士、仲野駿一修士、松尾宜朗修士、田中唯人学士を始め、千葉大学薬化学研究室の皆様に心より感謝致します。

生物活性評価を行って下さった、理化学研究所の袖岡幹子主任研究員、闥闥孝介専任研究員、並びに金田篤志教授を始めとした本学医学研究院分子腫瘍学研究室の皆様に厚く御礼申し上げます。

貴重なフィンランド留学を支援して下さった、タンペレ工科大学 Robert Franzén 教授に深く感謝致します。

各種スペクトル測定して頂いた本学分析センターの皆様に感謝致します。

社会人になっても変わらず接してくれた、右後ろの皆様に感謝致します。

研究室生活の合間の、貴重な息抜きに協力してくれた薬学野球部の皆様に感謝致します。

最後に、陰ながら私を支え、わがままを聞き入れてくれた家族に深く感謝致します。

2016 年 3 月

鈴木　雄太

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

主査　千葉大学大学院教授　薬学博士　西田　篤司
副査　千葉大学大学院教授　薬学博士　高山　廣光
副査　千葉大学大学院教授　薬学博士　石橋　正己