連続反応に基づく多環式天然物の合成研究

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化学・生命化学専攻　化学合成法研究

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略語表

^{2}Py	2-pyridyl
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Bn	benzyl
Bz	benzoyl
cat	catalytic amount
CuTC	copper(I) 2-thiophenecarboxylate
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
dig	digonal
diNO_2Bz	3,5-dinitrobenzoyl
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N'*-dimethylpropyleneurea
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTB	bis[di(3,5-di-*tert*-butylphenyl)phosphino]
DTBM	bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et	ethyl
equiv	equivalent
h	hour
HRMS	high resolution mass spectrometry
HMPA	hexamethylphosphoric triamide
IMDA	intramolecular Diels-Alder
*i*Pr	isopropyl

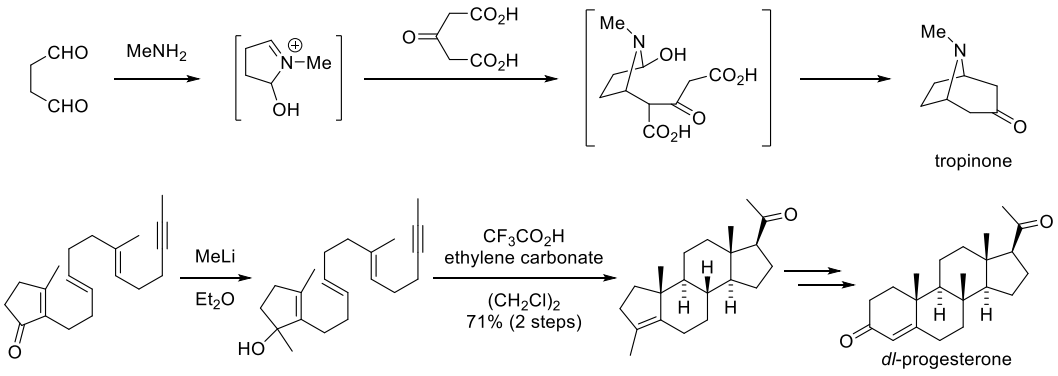
KHMDS	potassium bis(trimethylsilyl)amide
L-Selectride®	lithium tri-*sec*-butylborohydride
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
min	minute
mp	melting point
Ms	methanesulfonyl
MS	molecular sieve
NBS	*N*-bromosuccinimide
*n*Bu	*n*-butyl
NMO	*N*-methylmorpholine *N*-oxide
NOESY	nuclear Overhauser effect correlated spectroscopy
Oxone®	potassium peroxymonosulfate
Ph	phenyl
PIDA	iodobenzene diacetate
PMB	*p*-methoxybenzyl
PPA	polyphosphoric acid
PTSA	*p*-toluenesulfonic acid
quant	quantitative
R_f	retention factor
rt	room temperature
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
temp	temperature
*t*Bu	*tert*-butyl
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl, tetramethylsilane
Tol-BINAP	2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
TPAP	tetra-*n*-propylammonium perruthenate

目次

第 1 章　序論

人類は古来より身近な植物などを薬として利用できることを経験的に学び、民間療法として役立ててきた。学問の発達に伴い、自然界に産出するどの化合物が生物活性を示すか明らかにされ、現在も海や土中などあらゆる場所から新たな生物活性物質が発見されている。その生物活性物質を薬のリード化合物として利用するために、有機合成化学は欠かすことのできない学門分野であり、希少な化合物の供給や薬効の最適化に大きく貢献してきた。一方で、自然界に産出する天然物と呼ばれる有機化合物のなかでも、複雑な構造を持つ化合物を合成することは、人類の自然に対する挑戦であり、有機合成化学の力量を検証する機会にもなる。今日の化合物の製造においては、純粋なものを作ることのみならず、コストや効率・簡潔さも重視され、また、環境に優しい合成が必要とされている。加えて副作用低減の観点から、生体における受容体に特異的に作用する複雑な構造の医薬品が求められ、製造されている。こうした現状を踏まえ、複雑な構造を持つ化合物の量的供給を目指した効率的な連続反応を開発することは、有機化学の発展に寄与するものであると考え、研究に着手した。

Scheme 1.1. Example of Cascade Reaction for Natural Product Synthesis[1,2]



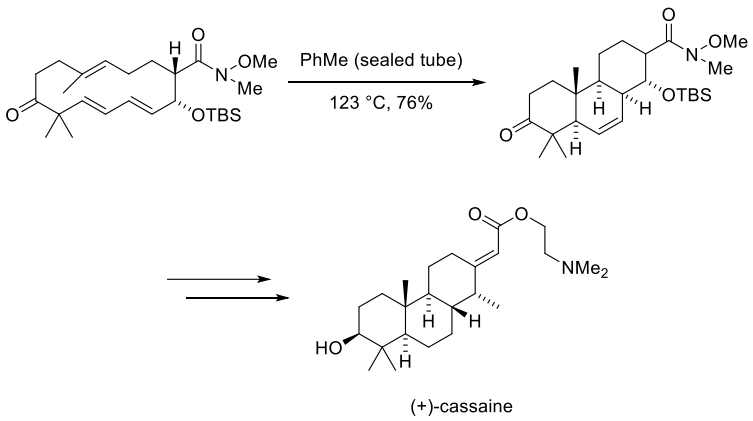
連続反応は、複数の反応を連続して進行させる手法であり、合成の効率化に有効な手法として認識されている。適切に基質をデザインすることで、一挙に多くの結合形成を行うことが可能であるため、天然物合成における骨格構築にもしばしば活用されてきた。その歴史は古く 1900 年初頭の Robinson による tropinone の合成[1]を皮切りに、今日までに様々な形式の連続反応と、それらを鍵とする全合成が報告されてきた**(Scheme 1.1)**。連続反応は系中で反応活性種を連鎖的に発生させるために、試薬の節約や単離操作の削減が可能なケースも多く、コストと手間を抑えることが可能となる。また、触媒を用いる連続反応の開発は、効率と有用性を高め、不斉触媒反応の開発にも繋がる。このような観点から、多環式天然物の骨格を構築する、新規な連続反応を開発することを研究の目的とした。

第 2 章　Liebeskind–Srogl カップリング/分子内 Diels–Alder 連続反応の開発

第 1 節　研究背景

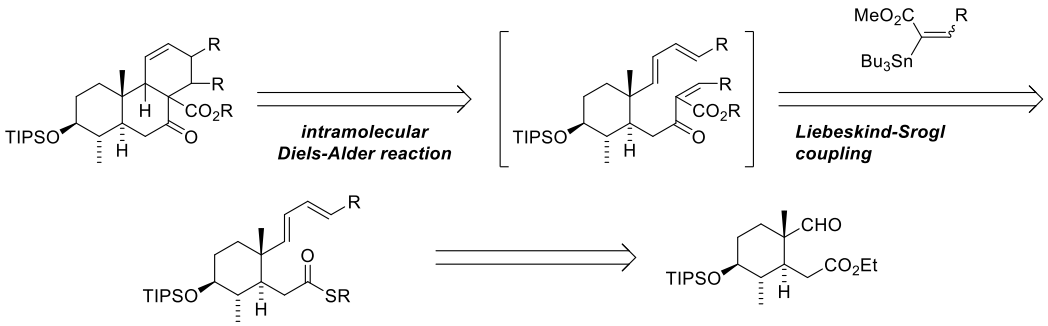
天然物合成において、分子内 Diels-Alder 反応（IMDA 反応）は環構築を行うための強力な手法である [3]。しかしながら、全炭素 4 級不斉中心の形成を伴う際には、ルイス酸の添加や加熱など厳しい条件を要することが多い(Scheme 2.1)。

Scheme 2.1. Example of IMDA Reaction (Deslongchamps, 2008)[4]



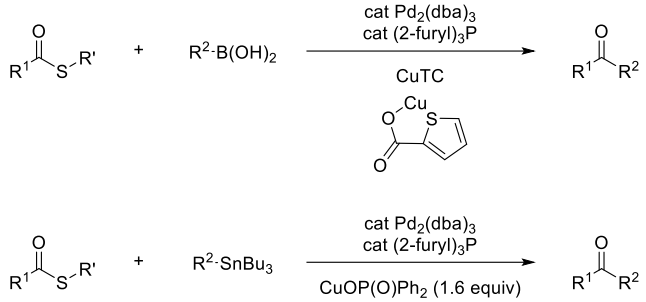
その環化反応を温和な条件下で行うために、環化基質の親ジエン部位を α-アルキリデン-β-ケトエステルとすることを計画した。すなわち、二つのカルボニル基によりアルケンを活性化することで、環化が容易に進行すると考えた。一方で、強く活性化された親ジエン部位は反応性の高さ故に不安定であることが懸念された。そこで、不安定であることが予想される α-アルキリデン-β-ケトエステルを単離することなく、IMDA 反応をワンポットで連続的に進行させることをねらった。(Scheme 2.2)。

Scheme 2.2. Plan of the Liebeskind-Srogl Coupling/IMDA Reaction Cascade



親ジエン部位の構築には、チオエステルとアルケニルスズ化合物を用いる Liebeskind-Srogl カップリングを選択した[5]。Liebeskind-Srogl カップリングは中性条件で進行する反応であり、酸や塩基に対し脆弱な化合物の反応に適している(Scheme 2.3)。

Scheme 2.3. Liebeskind-Srogl Coupling Reaction



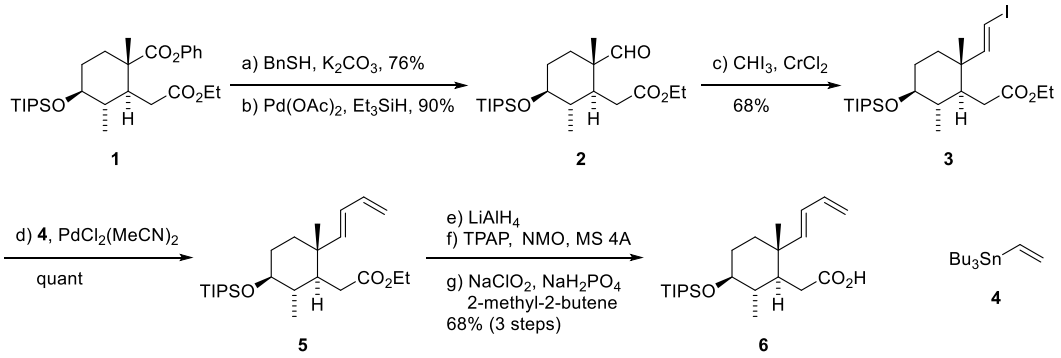
反応基質となるチオエステルは、当研究室で開発した 1,4-ヒドリド還元を起点とする連続 Michael 反応により、立体選択的に合成可能なジエステルを出発原料として合成した(Scheme 2.4)[6]。このアルデヒドが有する立体配置により、立体選択的な IMDA 反応が進行すると考えたためである。Liebeskind-Srogl カップリングを起点とする連続反応はこれまでに例がない。また、本連続反応により得られる三環式化合物は天然物合成における骨格構築に有効であると考え、研究に着手した。

Scheme 2.4. Highly Stereoselective Michael Reduction/Intramolecular Michael Reaction Cascade[6]

第 2 節　基質合成

反応検討を行うため、基質の合成に取り掛かった(Scheme 2.5)。連続 Michael 反応により得られる **1** を出発物として合成を開始し、エステル交換反応によるベンジルチオエステルへの変換、福山還元によりアルデヒド **2** を得た。しかし、得られたアルデヒドに対する直接的なジエンの導入（Wittig 反応、Julia-Kocienski 反応）は進行しなかった。そこで、高井-内本オレフィン化により、ヨードアルケン **3** を合成し、続いて tributylvinyltin **4** との Stille カップリングを行うことでジエン **5** を得た。**5** のエステル部位の加水分解を用いたカルボン酸への変換は、複雑な混合物を与えた。したがって、水素化アルミニウムリチウムによる還元、TPAP 酸化、Pinnick 酸化を経て、三工程で **5** からカルボン酸 **6** を合成した。

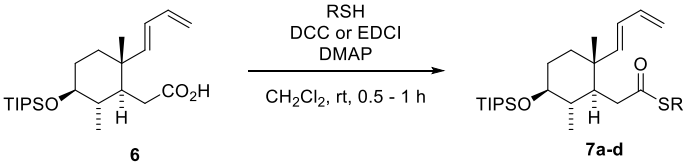
Scheme 2.5. Preparation of Carboxylic Acid **6**



Reagents and Conditions: (a) benzyl mercaptane, K_2CO_3, DMF, 60 °C, 4 h, 76%; (b) $Pd(OAc)_2$, Et_3SiH, acetone, rt, 10 min, 90%; (c) CHI_3, $CrCl_2$, 1,4-dioxane/THF, rt, 8 h, 68%; (d) **4**, $PdCl_2(MeCN)_2$, DMF, rt, 1 h, quant; (e) $LiAlH_4$, THF, 0 °C, 4 h; (f) TPAP, NMO, MS 4A, CH_2Cl_2, rt, 12 h; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, rt, 4 h, 68% (3 steps).

合成したカルボン酸 **6** を用いて、各種チオールと縮合反応を行い、反応基質となるチオエステル **7a-d** を合成した(Table 2.1)。

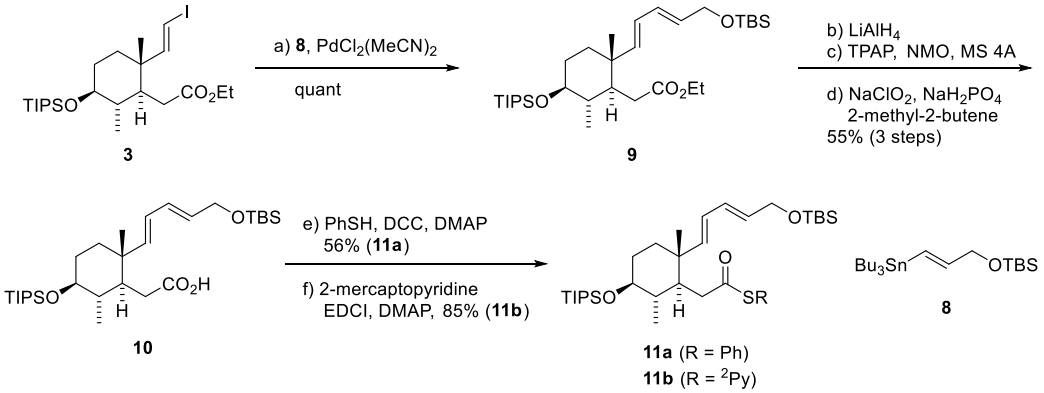
Table 2.1. Preparation of Thioesters **7a-d**



entry	R	reagent	yield (%)
1	Et (**7a**)	DCC	12
2	*t*Bu (**7b**)	DCC	35
3	Ph (**7c**)	DCC	87
4	^{2}Py (**7d**)	EDCI	98

続いて、基質一般性の確認のため、ジエン部位の末端に置換基を導入した基質を合成した(Scheme 2.6)。ヨードアルケン **3** とスズ化合物 **8**[7] との Stille カップリングを用いて、*tert*-butyldimethylsilyloxymethyl 基を有するジエン **9** を合成した。続いて、Scheme 2.5 と同様にエステルからカルボン酸への変換、Table 2.1 と同様の変換を施し、チオエステル **11a,b** を合成した。

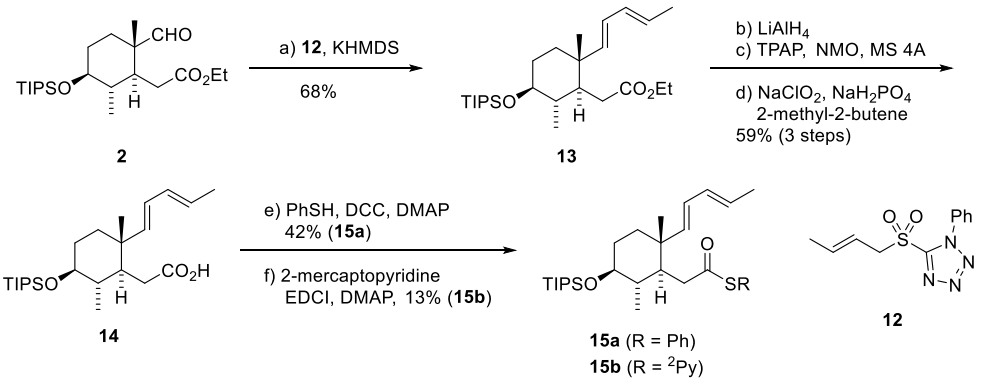
Scheme 2.6. Preparation of Thioesters **11a,b**



Reagents and Conditions: (a) **8**, $PdCl_2(MeCN)_2$, DMF, rt, 1 h, quant; (b) $LiAlH_4$, THF, 0 °C, 8 h; (c) TPAP, NMO, MS 4A, CH_2Cl_2, rt, 12 h; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, rt, 4 h, 55% (3 steps); (e) PhSH, DCC, DMAP, CH_2Cl_2, 2 h, 56%; (f) 2-mercaptopyridine, EDCI, DMAP, CH_2Cl_2, rt, 2 h, 85%.

次に、末端にメチル基を有するジエンを合成した(Scheme 2.7)。対応するスズ化合物の合成が困難であったため、Julia-Kocienski 反応によるジエン構築を行った。検討の結果、アルデヒド **2** に対して 3.0 当量の **12**[8] を用い、1,2-ジメトキシエタン溶媒下反応を行うことで、*E* 体ジエン **13** を立体選択的に得ることに成功した。同様の変換により、カルボン酸 **14** を合成した。続く、塩化メチレン溶媒下でのフェニルチオエステル **15a** への変換は 20%程度と低収率であったが、酢酸エチルを溶媒とすることで 42%と中程度の収率で目的物が得られることを見出した。一方、2-ピリジルチオエステル **15b** の合成は種々の反応条件を検討したが、低収率に留まった。

Scheme 2.7. Preparation of Thioesters **15a,b**

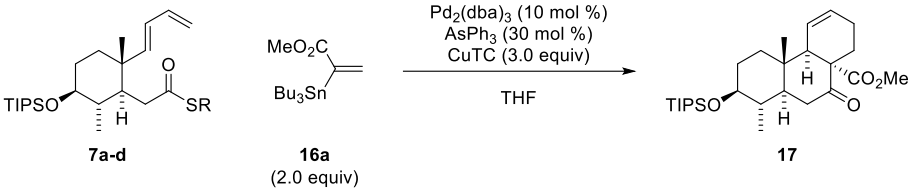


Reagents and Conditions: (a) **12**, KHMDS, DME, rt, 2 h, 68%; (b) $LiAlH_4$, THF, 0 °C, 8 h; (c) TPAP, NMO, MS 4A, CH_2Cl_2, rt, 16 h; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, rt, 24 h, 59% (3 steps); (e) PhSH, DCC, DMAP, EtOAc, rt, 15 min, 42%; (f) 2-mercaptopyridine, EDCI, DMAP, CH_2Cl_2, rt, 13%.

第 3 節　反応検討

反応基質となるチオエステルが合成できたため、連続反応の検討に着手した。まず、チオエステル **7a-d** と methyl 2-tributylstannylacrylate **16a**[9] との Liebeskind-Srogl カップリングを検討した(Table 2.2)。反応には、パラジウム触媒として tris(dibenzylideneacetone)dipalladium(0) を 10 mol %、配位子として triphenylarsine を 30 mol %使用し、さらに反応を促進する添加剤として copper(I) 2-thiophenecarboxylate (CuTC) を 3.0 当量加えた。アルキルチオエステル **7a,b** を基質としたとき、50 °C で反応を行っても反応は進行しなかった(Table 2.2, entries 1 and 2)。そこで、フェニルチオエステル **7c** を用いて反応を行うと、室温下、3 時間で原料は消失し、生成物を収率 58%で得ることに成功した(entry 3)。得られた化合物はカップリング反応のみならず IMDA 反応まで進行した三環式化合物 **17** であり、単一のジアステレオマーであった。さらに、2-ピリジルチオエステル **7d** を用いると、反応時間は 0.5 時間に短縮され、収率は 81%まで向上した(entry 4)。ピリジル基がパラジウム触媒に配位し、酸化的付加を促進したためであると考えている。

Table 2.2. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **7a-d** and **16a**



7a-d　　**16a** (2.0 equiv)　　**17**

entry	R	temp (°C)	time (h)	yield (%)
1	Et (**7a**)	rt, 50	2, 12	trace
2	*t*Bu (**7b**)	rt, 50	1, 12	NR
3	Ph (**7c**)	rt	3	58
4	^{2}Py (**7d**)	rt	0.5	81

本反応において、カップリング体である α-アルキリデン-β-ケトエステルは確認されなかったため、IMDA 反応は非常に早く進行したものと推察される。また、生成物の詳細な構造解析の結果、*trans-trans-cis* 縮環を有する化合物 **17** であることを確認した(Figure 2.1)。

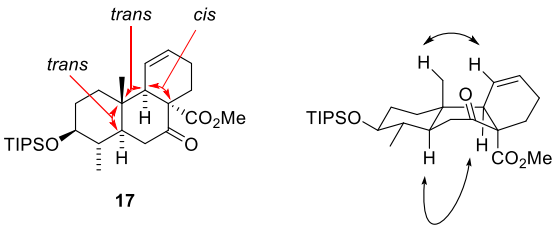


Figure 2.1. NOESY correlations in the NOESY spectrum of **17**.

このような立体選択性が発現した要因を反応遷移状態から考察した(Figure 2.2)[10]。ジエン部位と親ジエン部位、それぞれの 2 つの反応面があるため、4 つの遷移状態を考えた。まず、*TS1* と *TS2* を比較すると、*TS2* では遷移状態は一般的に安定な chair-chair 型となるが、エステル部位が縮環部位のメチル基と 1,3-diaxial 反発を起こすため不安定となるため、相対的に安定な chair-boat 型の *TS1* が有利となると考えた。また、keto-*endo* 型の *TS1* と ester-*endo* 型の *TS3* を比較すると、エステルよりも電子不足なケトンの方が軌道の二次的相互作用が強く働くために、*TS1* をとり、**17** が得られたと考察した。

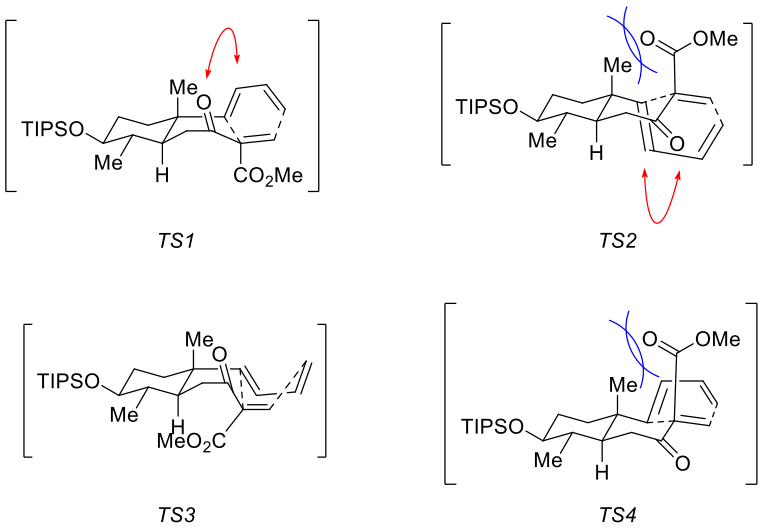
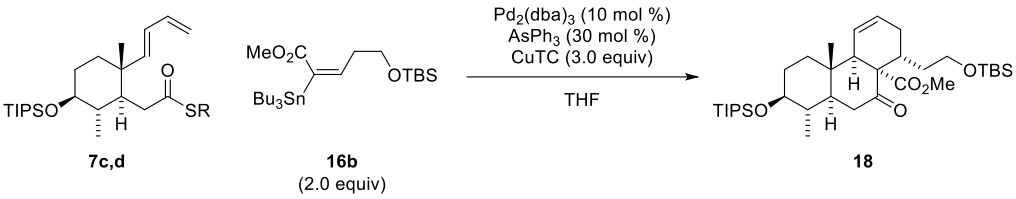


Figure 2.2. Plausible transition states of the IMDA reaction.

この結果を受け、基質一般性を確認するために、親ジエン部位に置換基を導入し、連続反応の検討を行った。親ジエン部位として、*E* 体および *Z* 体の三置換アルケニルスズ化合物を合成し、検討に用いた。*E* 体のアルケニルスズ化合物 **16b**[11] を用いて反応を行った場合、フェニルチオエステル **7c** との反応では、2 時間で原料は消失し、三環式化合物 **18** を収率 66%で得た(Table 2.3, entry 1)。一方、2-ピリジルチオエステル **7d** との反応は 0.5 時間で原料は消失するものの、収率は 44%に留まった(etnry 2)。**Table 2.2** と異なりフェニルチオエステル **7c** が反応に適していた理由は、三置換アルケニルスズとの Liebeskind-Srogl カップリングは遅いため、より反応性の高い 2-ピリジルチオエステルあるいはそのアシルパラジウム種が反応系中で分解するためであると考えている。

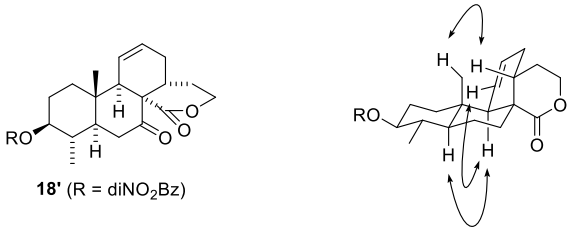
単結晶 X 線構造解析による絶対立体配置決定のために、油状物質 **18** の変換を行った。結晶性を高めることを目的として、ジニトロベンゾイル基を有する **18'**へと変換したが、単結晶を得ることはできなかった。そのため、NOESY 解析によって **18'**の立体配置が **17** と同様、*trans-trans-cis* であることを確認した(Figure 2.3)。

Table 2.3. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **7c,d** and **16b**



7c,d **16b** (2.0 equiv) **18**

entry	R	time (h)	yield (%)
1	Ph (**7c**)	2	66
2	^{2}Py (**7d**)	0.5	44

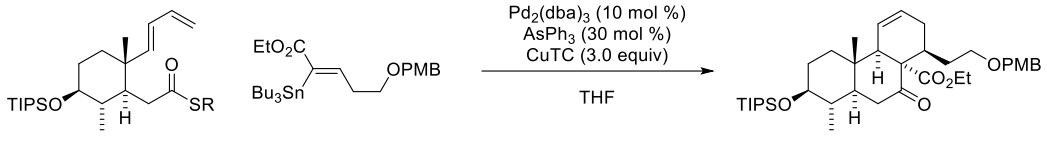


18' (R = diNO$_2$Bz)

Figure 2.3. NOESY correlations in the NOESY spectrum **18'**.

続いて、*Z* 体のアルケニルスズ化合物 **16c**[12] を用い、反応を行った(Table 2.4)。フェニルチオエステル **7c** との反応は、収率 31%で生成物を得ることに成功した(entry 1)。しかし、2-ピリジルチオエステル **7d** との反応は痕跡量の生成物が確認されるのみであった(entry 2)。得られた化合物の構造解析は、二工程の変換の後行い、**17**、**18** と同様の相対立体配置を有することを確認した(Figure 2.4)。

Table 2.4. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **7c,d** and **16c**



7c,d **16c** (2.0 equiv) **19**

entry	R	time (h)	yield (%)
1	Ph (**7c**)	2	31
2	^{2}Py (**7d**)	0.5	trace

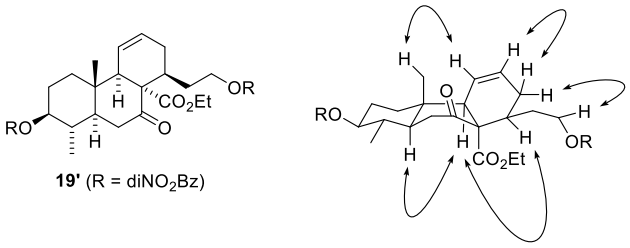
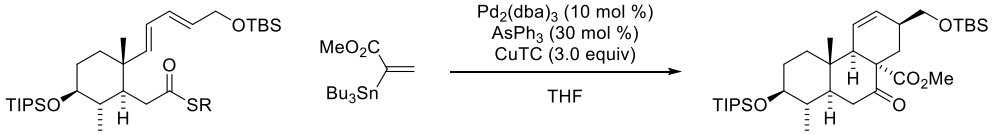


Figure 2.4. NOESY correlations in the NOESY spectrum of **19'**.

続いて、ジエン部位に置換基を導入した反応基質を用いて検討を行った。まず、*tert*-butyldimethylsilyloxymethyl 基を導入したジエン **11a,b** と置換基を持たないアルケニルスズ化合物 **16a** を用いた(Table 2.5)。フェニルチオエステル **11a** を用いたとき、10 時間で原料は消失し、収率33%で生成物を得た(entry 1)。2-ピリジルチオエステル **11b** を用いたとき、2 時間で原料消失を確認し、収率は 62%に向上した(entry 2)。その構造は、*trans-trans-cis* 縮環を持つ **20** であることを確認した(Figure 2.5)。

Table 2.5. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **11a,b** and **16a**



11a,b **16a** **20**

entry	R	time (h)	yield (%)
1	Ph (**11a**)	10	33
2	^{2}Py (**11b**)	2	62

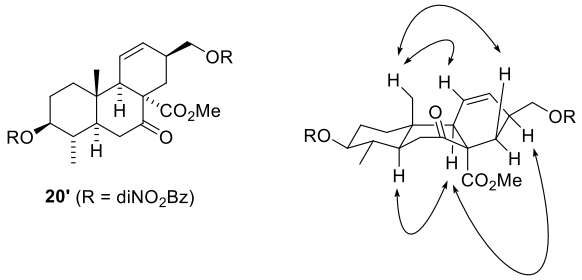
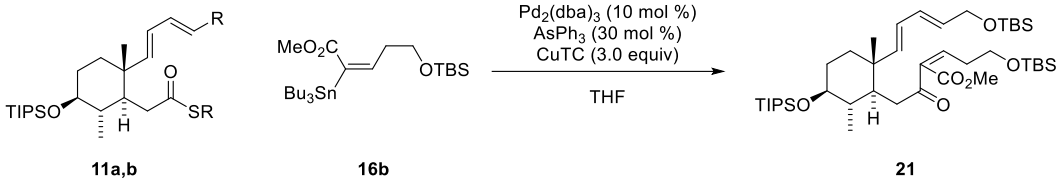


Figure 2.5. NOESY correlations in the NOESY spectrum of **20'**.

また、**11a,b** と置換基を導入したアルケニルスズ化合物 **16b,c** との反応も行った。

E 体のアルケニルスズ化合物 **16b** との反応において、フェニルチオエステル **11a** および 2-ピリジルチオエステル **11b**、いずれの基質においてもカップリング体 **21** のみが得られ、環化体は得られなかった(Table 2.6, entries 1 and 2)。電子求引性基である *tert*-butyldimethylsilyloxymethyl 基の影響により、IMDA 反応が阻害されたと考えられる。単離精製を行ったカップリング体 **21** に対して加熱やルイス酸による環化を試みたが、原料が分解するのみであり、環化体を得ることはできなかった。

Table 2.6. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **11a,b** and **16b**

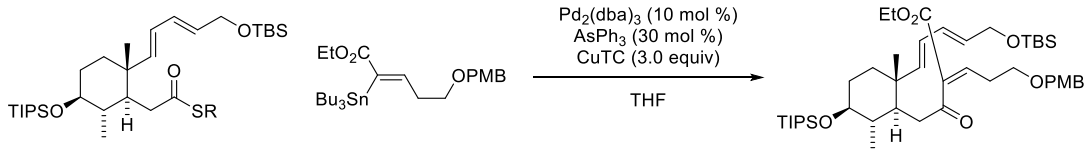


11a,b **16b** (2.0 equiv) **21**

entry	R	time (h)	yield (%)
1	Ph (**11a**)	3	58
2	^{2}Py (**12b**)	0.5	<53

Z 体のアルケニルスズ化合物 **16c** とのカップリングも行った(Table 2.7)。フェニルチオエステル **11a** との反応では収率 46%で生成物が得られるものの、環化体ではなくカップリング体 **22** であった(entry 1)。一方、2-ピリジルチオエステル **11b** との反応では生成物はほとんど得られなかった(entry 2)。

Table 2.7. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **11a,b** and **16c**

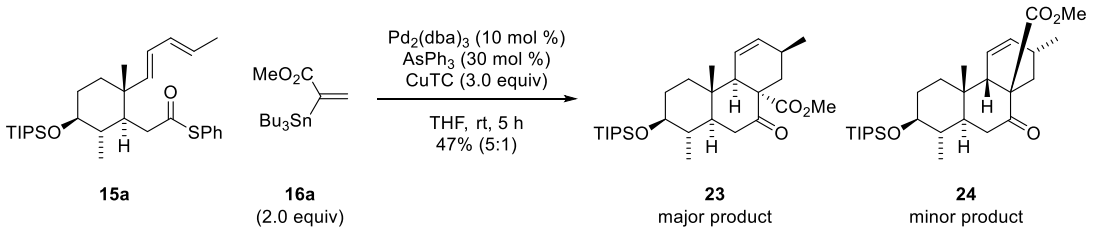


11a,b **16c** (2.0 equiv) **22**

entry	R	time (h)	yield (%)
1	Ph (**11a**)	4	46
2	^{2}Py (**11b**)	4	trace

続いて、ジエン部位にメチル基を導入した基質 **15a** を用いて、同様の検討を行った(Scheme 2.8)。フェニルチオエステル **15a** とアルケニルスズ化合物 **16a** との反応は、5 時間で原料の消失を確認した。生成物は分離困難な異性体の混合物であり、その比率は 5:1 であった。二工程の変換の後、二つの異性体を分離し、構造決定を行った。その結果、主生成物が **23** であり、副生成物が **24** であると確認できた(Figure 2.6 and 2.7)。化合物 **24'**におけるジエン末端のメチル基に由来する部位は NOESY 解析から決定できなかったため、IMDA 反応の遷移状態から推測した。

Scheme 2.8. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **15a** and **16a**



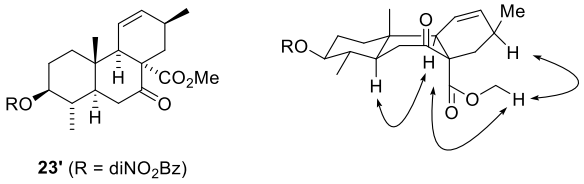


Figure 2.6. NOESY correlations in the NOESY spectrum of **23'**.

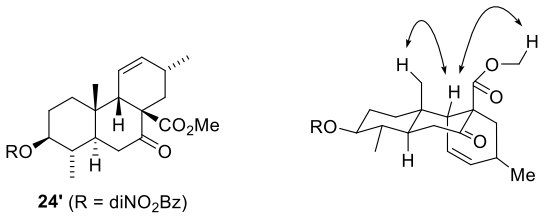
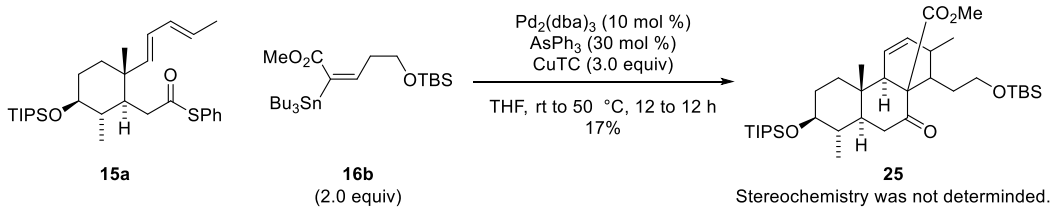


Figure 2.7. NOESY correlations in the NOESY spectrum of **24'**.

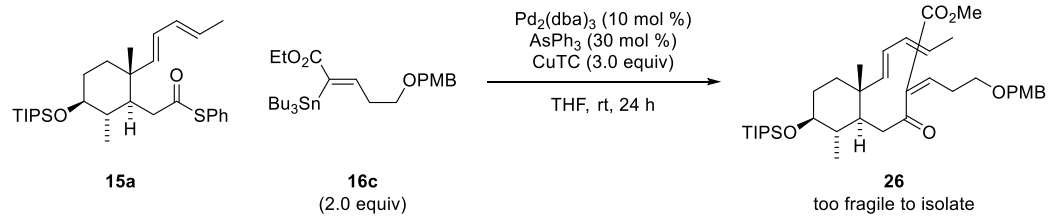
また、**15a** と *E* 体のアルケニルスズ化合物 **16b** とのとの反応も行った(Scheme 2.9)。その結果、室温で反応は進行し生成物を得たが、カップリング体と環化体の混合物であった。そのため、カップリング反応の終了を確認した後、50 ℃ に昇温し、さらに反応を続けたところ、環化体 **25** を収率 17%で得ることに成功した。しかしながら、得られた環化体が微量であったため、構造決定には至っていない。この基質において、環化が進行した要因は、メチル基の導入によりジエン部位の電子密度が増加したためであると考えている。

Scheme 2.9. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **15a** and **16b**



また、*Z* 体のアルケニルスズ化合物 **16c** との反応も行った(Scheme 2.10)。室温においてカップリングは進行したが、生成物 **26** は構造不明の化合物との混合物であった。また、得られたカップリング体は不安定であり、単離困難であった。

Scheme 2.10. Liebeskind-Srogl Coupling/IMDA Reaction Cascade of **15a** and **16c**



以上の検討から、Liebeskind-Srogl カップリング/IMDA 連続反応の開発により、三環式化合物を立体選択的に得ることに成功した。二置換アルケンとの反応には 2-ピリジルチオエステルが適していた。配位性を有するピリジル基がパラジウム触媒の酸化的付加を促進するためであると考えている。一方、三置換アルケンとの反応にはフェニルチオエステルが適していた。三置換アルケンとの Liebeskind-Srogl カップリングは遅く、より反応性の高い 2-ピリジルチオエステルは反応系中で分解するためであると考えている。また、ジエンあるいはアルケンのいずれかに置換基を導入した場合には環化反応が進行するが、両方に置換基を導入すると環化反応が困難になることを見出した。本反応の特長は、前例のない Liebeskind-Srogl カップリングを起点とする連続反応であること、三環式化合物を立体選択的に構築可能であることである。得られた *trans-trans-cis* 縮環を持つ三環式化合物は kaurane 類や atisene 類の合成へ応用することが可能であると考えている(Figure 2.8)。

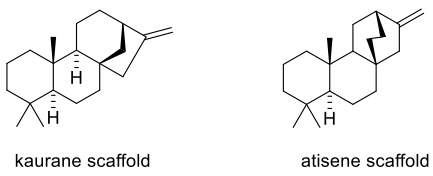


Figure 2.8. Natuarl Products

第 3 章　エナンチオ選択的 1,6-エンイン環化異性化反応の開発

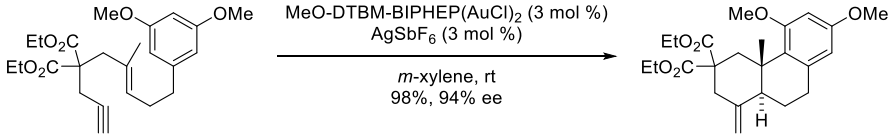
第 1 節　研究背景

1,6-エンイン環化反応などのポリエン環化はステロイド類の生合成仮説に端を発し、実験的にも研究され、発展を遂げてきた [13]。現在では、様々な官能基を反応開始部位とするポリエン環化が開発され、天然物合成にも応用されている [14]。ポリエン環化を用いると、複数の不斉中心を一挙に立体選択的に構築可能である。

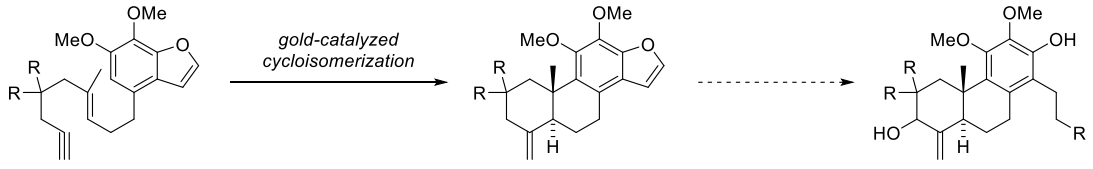
本研究では、1,6-エンイン環化の起点として、金触媒を用いることを計画した。多くの金触媒は空気中で安定に存在し、取り扱いが容易である。しかし、銀塩を用いてカチオン性錯体を形成すると高い反応性を示す。カチオン性金錯体はπ酸としてアルキンを活性化し、各種求核剤（アルコール、アミン、アルケン等）の付加を誘起する [15]。同様のπ酸性をもつ水銀と比べ毒性が小さく、白金より穏和な条件で反応が進行するという利点がある。

金触媒は不斉配位子を用いることでエナンチオ選択的な反応への応用が可能であり、Toste らはホスフィン配位子を用いた金(I)二核錯体によって、高収率かつ高エナンチオ選択的な 1,6-エンイン環化を報告している(Scheme 3.1)[16]。しかしながら、基質適用範囲は未だ明らかにされておらず、収率・エナンチオ選択性ともに優れた反応は少ないため、その探索・改良の余地は多く残されている。そこで、電子豊富なベンゾフランを反応停止部位とする 1,6-エンイン環化異性化を計画した(Scheme 3.2)。本反応により得られる三環式化合物のベンゾフラン部位は開環することでアルキル鎖へ変換可能であり、エキソメチレンは酸化反応の足掛かりとなるため、天然物合成に有用であると考えた。また、これまでにベンゾフランを反応停止部位とした基質の反応例はない。

Scheme 3.1. Catalytic Enantioselective 1,6-Ene-Yne Cycloisomerization (Toste, 2010)



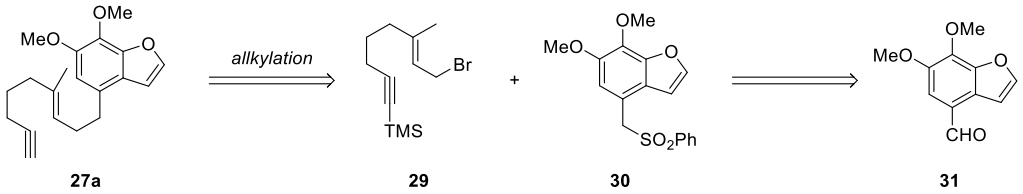
Scheme 3.2. Plan of 1,6-Ene-Yne Cycloisomerization



第 2 節　ジアステレオ選択的 1,6-エンイン環化異性化

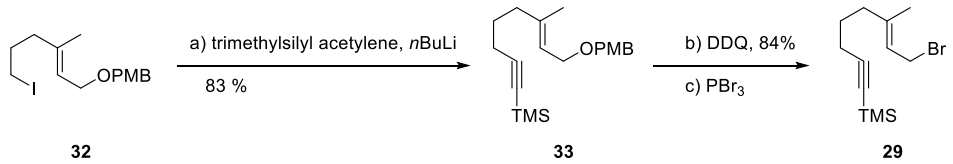
1,6-エンイン環化異性化を行うための基質合成に取り掛かった。環化基質 **27a** は A 環部位に官能基を持たないため、エキソメチレンを足掛かりとした酸化度の調節が容易である。そのため、様々な天然物合成へ応用可能であると考え、設定した。**27a** は臭化物 **29** とスルホン **30**、二つのフラグメントのカップリングにより得られると考えた(Scheme 3.3)。また、スルホン **30** は既知化合物 **31** から変換可能であると計画した。

Scheme 3.3. Retrosynthetic Analysis of **27a**



臭化物 **29** の合成経路を記す(Scheme 3.4)。文献既知の **32**[17] に対するリチウムアセチリドの付加によりアルキンを導入した **33** を合成した。DDQ を用いて PMB 基の脱保護を行った後、三臭化リンを作用させ、**29** を合成した(Scheme 3.4)。

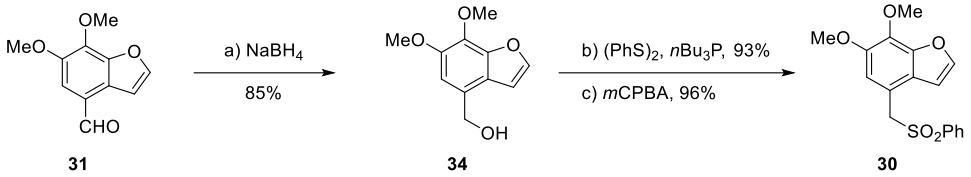
Scheme 3.4. Preparation of Bromide **29**



Reagents and Conditions: (a) trimethylsilyl acetylene, *n*BuLi, THF, rt, 12 h, 83%; (b) DDQ, CH_2Cl_2, rt, 2 h, 84%; (c) PBr_3, Et_2O, 0 °C, 30 min, quant.

また、文献既知のベンゾフラン **31**[18] を原料にスルホン **30** の合成を行った(Scheme 3.5)。**31** のホルミル基を、水素化ホウ素ナトリウムを用いて還元し、アルコール **34** を得た。アルコールをスルフィドへと変換し、*m*CPBA を用いた酸化によってスルホン **30** を合成した。

Scheme 3.5. Preparation of Sulfone **30**

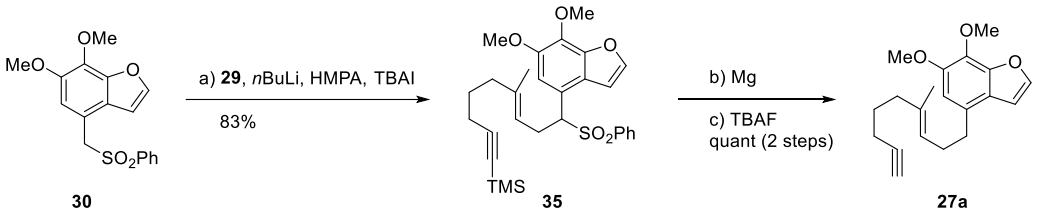


31 **34** **30**

Reagents and Conditions: (a) $NaBH_4$, MeOH, 0 °C, 30 min, 85%; (b) diphenyl disulfide, tri-*n*-butyl phosphine, THF, rt, 2 h, 93%; (c) *m*CPBA, CH_2Cl_2, 0 °C, 1 h, 96%.

二つのフラグメント **29** および **30** が調製出来たため、*n*BuLi を用いてカップリングを行った(Scheme 3.6)。続いて、マグネシウムを用いたスルホニル基の除去 [19]、TBAF を用いたトリメチルシリル基の脱保護により、環化基質 **27a** の合成に成功した。

Scheme 3.6. Preparation of Substrate **27a**

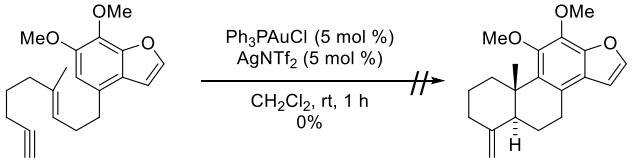


30 **35** **27a**

Reagents and Conditions: (a) **29**, *n*BuLi, HMPA, TBAI, THF, rt, 18 h, 83%; (b) Mg, MeOH, rt, 4 h; (c) TBAF, THF, rt, 1 h, quant (2 steps).

環化基質の合成に成功したため、環化異性化反応を行った(Scheme 3.7)。chloro(triphenylphophine)gold(I) (5 mol %) と silver bis(trifluoromethanesulfonyl)imide (5 mol %) から反応系中で生成したカチオン性金錯体を作用させたところ、原料 **27a** は消失し複数の生成物が得られた。構造解析を行った結果、いずれも目的物ではなかったため、環化基質の再考を行った。

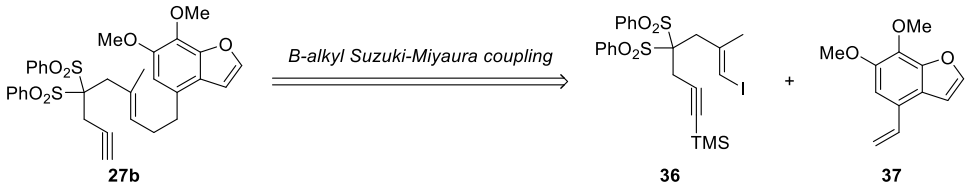
Scheme 3.7. Attempted Gold(I)-Catalyzed Cycloisomerization of **27a**



27a **28a**

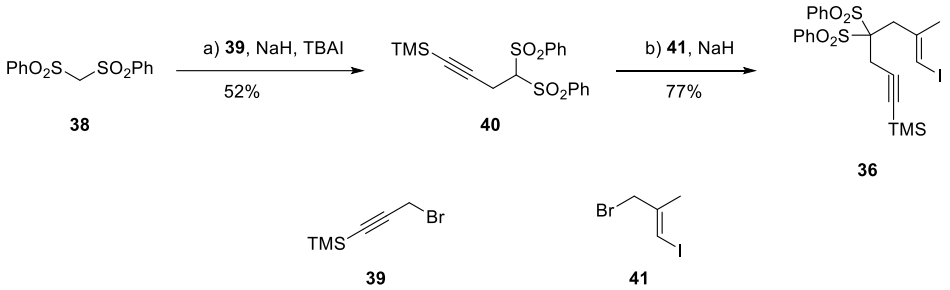
環化異性化により複数の生成物が得られた原因として、炭素鎖の自由度による影響が考えられたため、Thorpe-Ingold 効果による立体配座制御および環化反応の促進を期待し、置換基の導入を計画した(Scheme 3.8)[20]。その置換基には容易に除去可能なフェニルスルホニル基を選択した。環化基質 **27b** は **36** と **37** の *B*-アルキル型鈴木-宮浦カップリングにより得られると考えた[21]。

Scheme 3.8. Retrosynthetic Analysis of Substrate **27b**



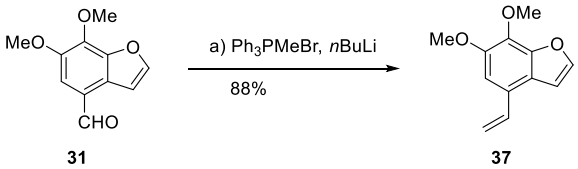
フェニルスルホニル基を有する環化基質は以下の様に合成した。まず、ビスフェニルスルホニルメタン **38** に対し、臭化プロパルギル **39**、臭化物 **41**[22] を順次反応させ、ヨウ化物 **36** を調製した(Scheme 3.9)。また、ベンゾフラン **31** のホルミル基を Wittig 反応によりアルケン **37** へと変換した(Scheme 3.10)。

Scheme 3.9. Preparation of Iodide **36**



Reagents and Conditions: (a) **39**, NaH, TBAI, THF, rt, 16 h, 52%; (b) **41**, NaH, THF, rt, 16 h, 77%.

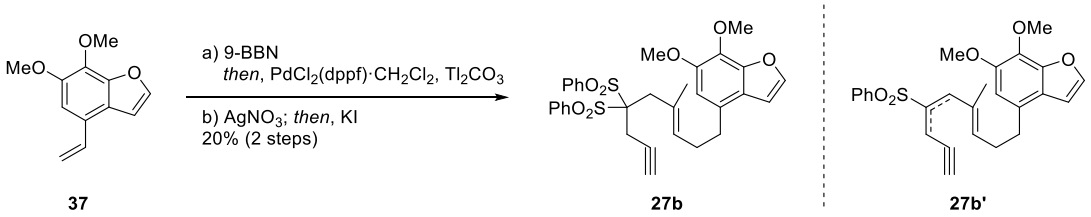
Scheme 3.10. Preparation of **37**



Reagents and Conditions: (a) Ph_3PMeBr, *n*BuLi, THF, 0 °C, 88%.

得られた二つのフラグメント **36**, **37** を用いて、*B*-アルキル型鈴木-宮浦カップリングを行った(Scheme 3.11)。検討の結果、有機溶媒に不溶かつ弱塩基性の炭酸タリウムを塩基として用いた場合のみ反応が進行することを見出した[23]。続くトリメチルシリル基の脱保護は、TBAF や炭酸カリウムを用いる塩基性条件ではスルホニル基の脱離が確認された(**27b'**)。そのため、硝酸銀を用いて中性条件で脱保護を行うことで、環化基質の合成に成功した[24]。

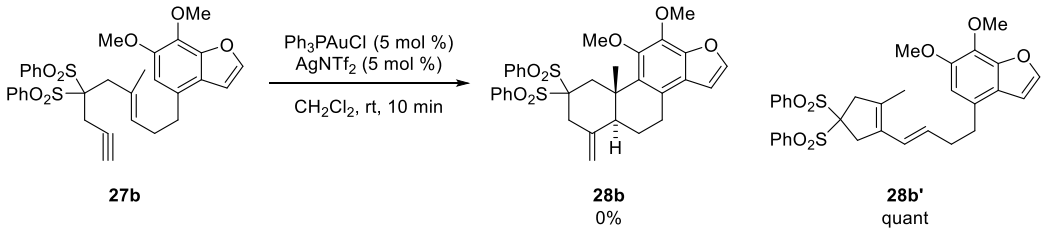
Scheme 3.11. Preparation of Substrate **27b**



Reagents and Conditions: (a) 9-BBN, THF, 2 h; **36**, $PdCl_2(dppf)\cdot CH_2Cl_2$, Tl_2CO_3, rt, 24 h; (b) $AgNO_3$, THF/EtOH/H_2O, rt, 1 h; KI, rt, 1 h, 20% (2 steps).

新たに合成した基質 **27b** を用いて、同様の条件で 1,6-エンイン環化異性化を検討した(Scheme 3.12)。その結果、単一の生成物が定量的に得られた。しかし、所望の化合物 **28b** ではなく、エンインメタセシスを経由して生じる 5 員環を有する化合物 **28b'**であった。

Scheme 3.12. Gold(I)-Catalyzed Cycloisomerization of **27b**



期待した環化異性化が進行しない原因はフェニルスルホニル基の嵩高さにあると考えた。すなわち、ポリエン環化反応において提唱される 6 員環遷移状態を取る際に、嵩高いスルホニル基とメチル基との間に 1,3-diaxial 反発が生じるため、5 員環を形成する反応経路により進行したと推測した(Figure 3.1)。

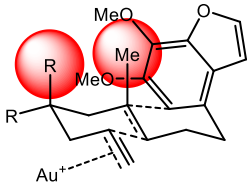
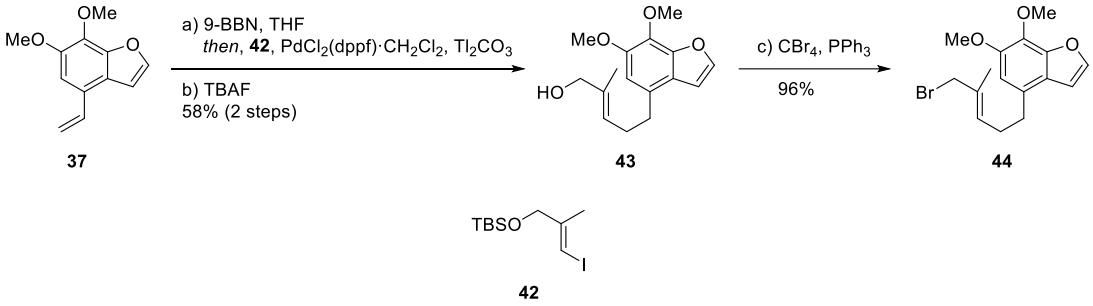


Figure 3.1. Plausible transition state of 1,6-ene-yne cycloisomerization

したがって、より小さな置換基であるメトキシカルボニル基やシアノ基に置き換えた基質で反応を試みるべく、基質合成に取りかかった(Scheme 3.13)。鈴木-宮浦カップリングを用いた基質 **27b** の合成が低収率であった原因として、ヨウ化物 **36** の塩基に対する脆弱性が考えられたため、新たな合成経路を選択した。ヨウ化物 **42**[25] を用い、鈴木-宮浦カップリングと脱保護を行うことで中程度の収率で **43** を得ることに成功した。得られたアルコールに Appel 反応を行い、共通中間体 **44** を合成した。

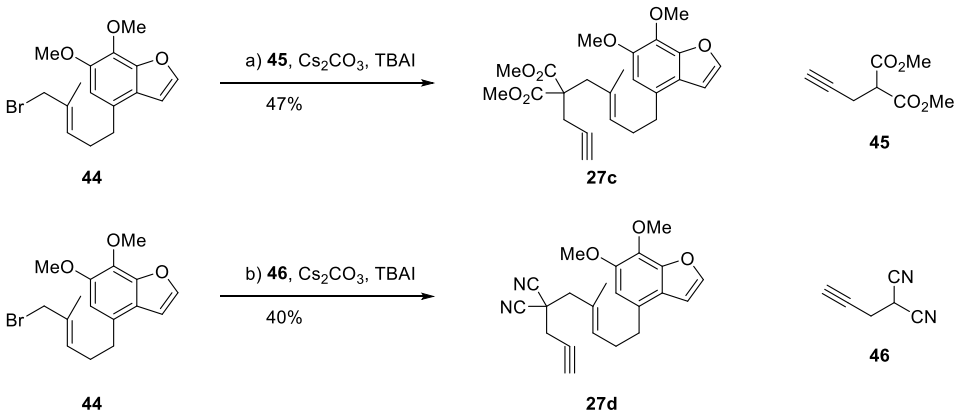
Scheme 3.13. Preparation of Bromide **44**



Reagents and Conditions: (a) 9-BBN, THF, 2 h; **42**, $PdCl_2(dppf)\cdot CH_2Cl_2$, Tl_2CO_3, rt, 24 h; (b) TBAF, THF, rt, 1 h, 58% (2 steps); (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 96%.

得られた臭化物 **44** に対してジエステル **45**[26]、ビスニトリル **46**[27] を反応させることで環化基質 **27c,d** を合成した(Scheme 3.14)。このとき溶媒として、エステル **27c** の合成にはアセトンが、ニトリル **27d** の合成にはアセトニトリルが適していた。

Scheme 3.14. Preparation of Substrates **27c**,**d**



Reagents and Conditions: (a) **45**, Cs_2CO_3, TBAI, acetone, rt, 16 h, 47%; (b) **46**, Cs_2CO_3, TBAI, MeCN, rt, 16 h, 40%.

基質合成に成功したため、環化異性化反応の検討を行った(Scheme 3.15)。エステル部位を有する基質 **27c** を用いた場合、所望の環化体 **28c** が、末端アルケンが内部アルケンへと異性化した **28c"**との混合物として得られることを見出した。この異性化反応は系中で生成する酸の影響によるものと考えている。しかし、5 員環を有する化合物 **28c'**も収率 57%で得た。一方で、シアノ基を有する基質を用いた場合、目的生成物 **28d** の異性化を伴うことなく単一の生成物として立体選択的に得ることに成功した。得られた生成物 **28d** は NOESY 解析により *trans* 縮環を持つことを確認した(Figure 3.1)。

Scheme 3.15. Gold(I)-Catalyzed Cycloisomerization of **27c,d**

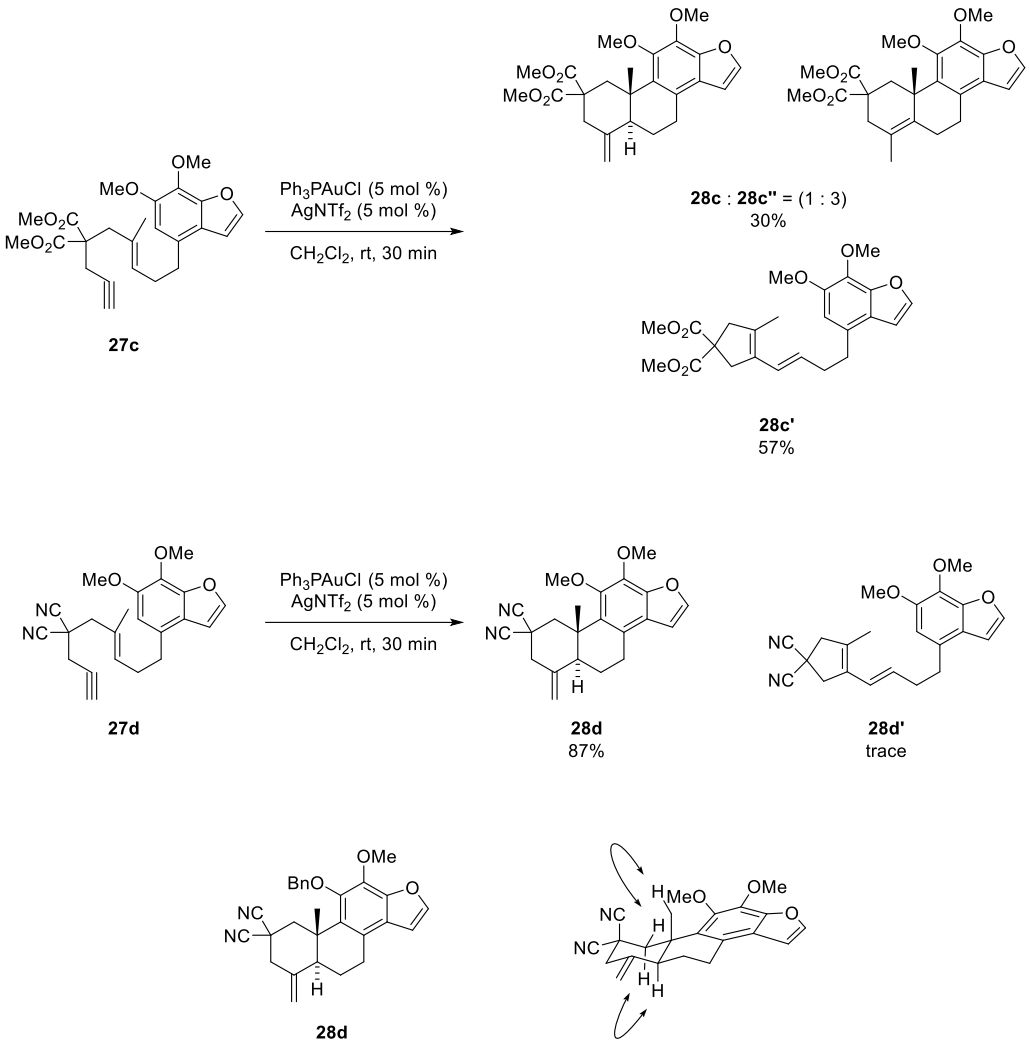


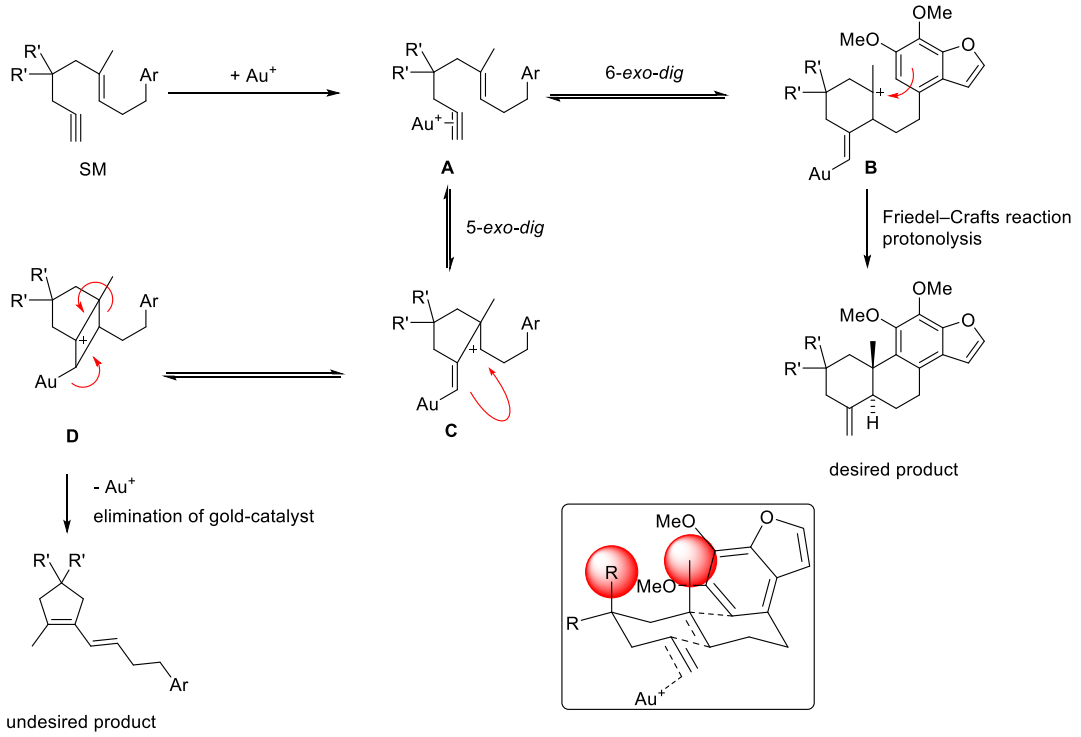
Figure 3.1. NOESY correlations in the NOESY spectrum of **28d**.

以上の実験結果を踏まえ、1,6-エンイン環化異性化の反応機構を考察した(Scheme 3.16)[28]。Thorpe-Ingold 効果のために導入した置換基の影響について考察する。本反応は、末端アルキンに対し、カチオン性金錯体が配位した **A** が生成することで開始する。

活性化されたアルキンに対し、6-*exo-dig* 型の環化が進行し、カルボカチオン **B** の形成を経て、芳香族求電子置換反応が起こることで、目的生成物が生成する。あるいは協奏的に反応が進行し、一挙に二環が生成した後に脱プロトン化することで目的物が得られる。

一方、5-*exo-dig* 型の環化が進行すると、カルボカチオン **C** が生成する。続けてカルボカチオンが転位し、**D** を経由し、金触媒が脱離を伴いつつ 5 員環化合物が得られる。5-*exo-dig* 型の環化が進行する原因は、置換基の嵩高さにあると考えている。スルホニル基のような嵩高い置換基を有する基質では 1,3-diaxial 反発により、6 員環遷移状態が不安定化されると考えられる。また、スルホニル基同士の立体反発により、結合角が狭まっていることも原因のひとつとして挙げられる。

Scheme 3.16. Plausible Mechanism of the Gold(I)-Catalyzed Cycloisomerization



シアノ基の導入により目的の環化生成物が選択的に得られることを見出したが、Tosteらの報告によると、反応条件は異なるが、エステル部位を有する基質においても、6-*exo-dig*型の環化生成物が選択的に得られている(Scheme 3.1)[16]。その基質の差異として反応停止部位の芳香環が

(1) 対称性を有するか

(2) 主鎖に対するパラ位に電子供与基を有するか

が挙げられる(Figure 3.2)。そこで、これら二つの要因が環化異性化反応に与える影響を調査すべく新たに基質 **47c,d**、**48** を設定し、同一反応条件での比較検討を計画した。

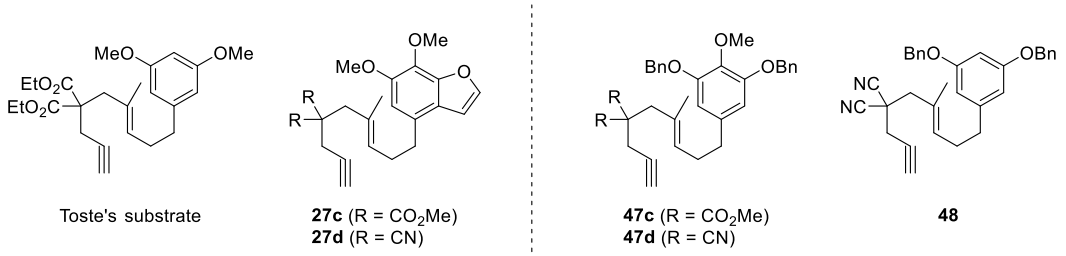
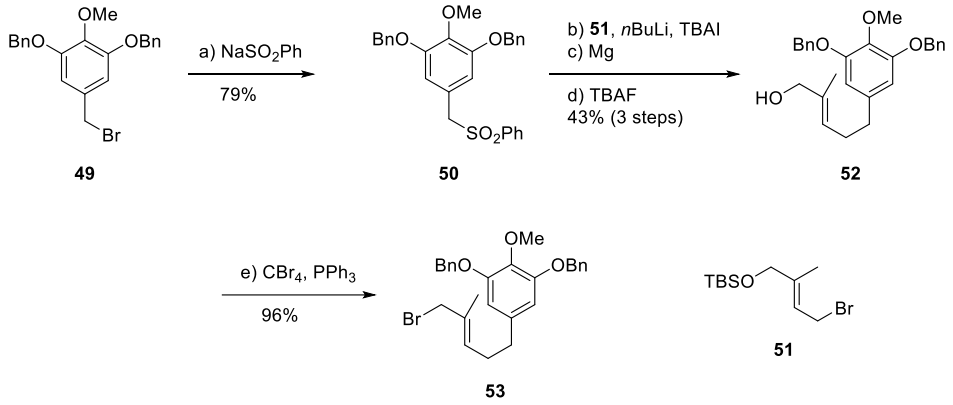


Figure 3.2. Comparison of substrates and new substrates

まず、環化基質 **47c,d** の合成に取り掛かった(Scheme 3.16)。対称性を持つ臭化ベンジル **49**[29] を原料とし、スルホニル化により **50** を得た。続けて、**50** を用いた **51**[30] とのアルキル化、スルホニル基と保護基の除去によりアルコール **52** を合成した。最後に、臭素化を行い、共通中間体 **53** を合成した。

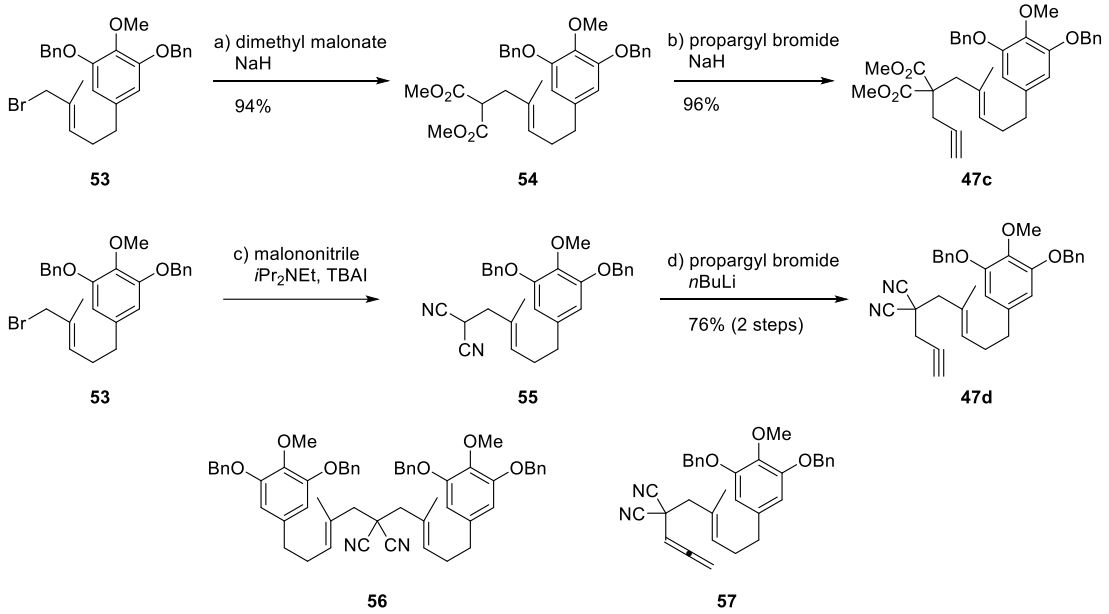
Scheme 3.16. Preparation of Common Intermediate **53**



Reagents and Conditions: (a) $NaSO_2Ph$, DMF, rt, 2 h, 79%; (b) **51**, *n*BuLi, TBAI, THF/DMPU, rt, 16 h; (c) Mg, MeOH, rt, 2 h; (d) TBAF, THF, rt, 1 h, 43% (3 steps); (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 96%.

得られた臭化物 **53** に対してジメチルマロネートを反応させ、**54** を合成した(Scheme 3.17)。続けて、プロパルギル化を行い、環化基質 **47c** を合成した。そこで、シアノ基を有する基質も同様に合成を試みた。しかし、**54** の合成と同様に水素化ナトリウムを用いると、過剰量のマロニトリルを用いた場合でも、**55** ではなく二つアルキル化された **56** が主生成物として得られることが問題となった。そこで、ジイソプロピルエチルアミンを塩化メチレン溶媒中用いることで、選択的に **55** を得ることに成功した。ジイソプロピルアミンの嵩高さが有効に作用したと思われる。続く、プロパルギル化は塩基として、水素化ナトリウムを用いるとアレン **57** への異性化が観測されたため、*n*BuLi を用い **47d** の合成に成功した。

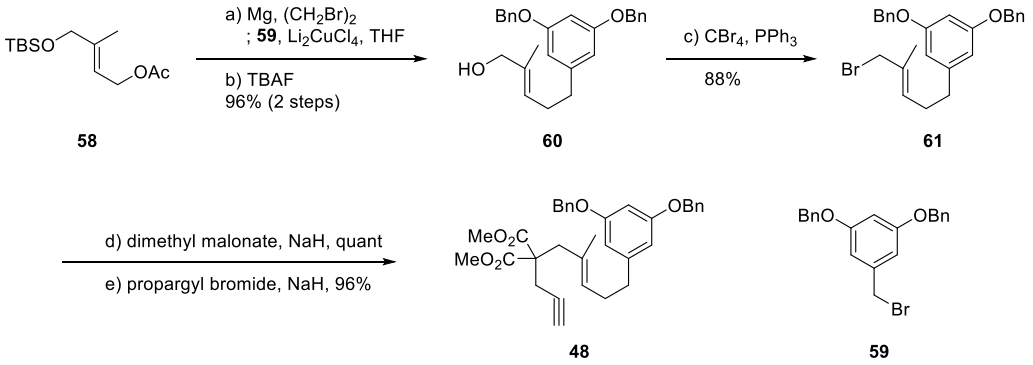
Scheme 3.17. Preparation of Substrate **47c,d**



Reagents and Conditions: (a) dimethyl malonate, NaH, THF, rt, 24 h, 54%; (b) propargyl bromide, NaH, THF, rt, 2 h, 96%; (c) malononitrile, *i*Pr$_2$NEt, TBAI, CH_2Cl_2, rt, 24 h; (d) propargyl bromide, *n*BuLi, THF, rt, 2 h, 76% (2 steps).

続いて、環化基質 **48** の合成を行った(Scheme 3.18)。臭化ベンジル **59**[31] から調製した Grignard 試薬と酢酸プレニル **58**[32] を銅触媒存在下、反応させることでカップリング体を得た[33]。続けて脱保護を行い、アルコール **60** を合成した。**60** に対して Scheme 3.17 と同様の変換により環化基質 **48** を合成した。

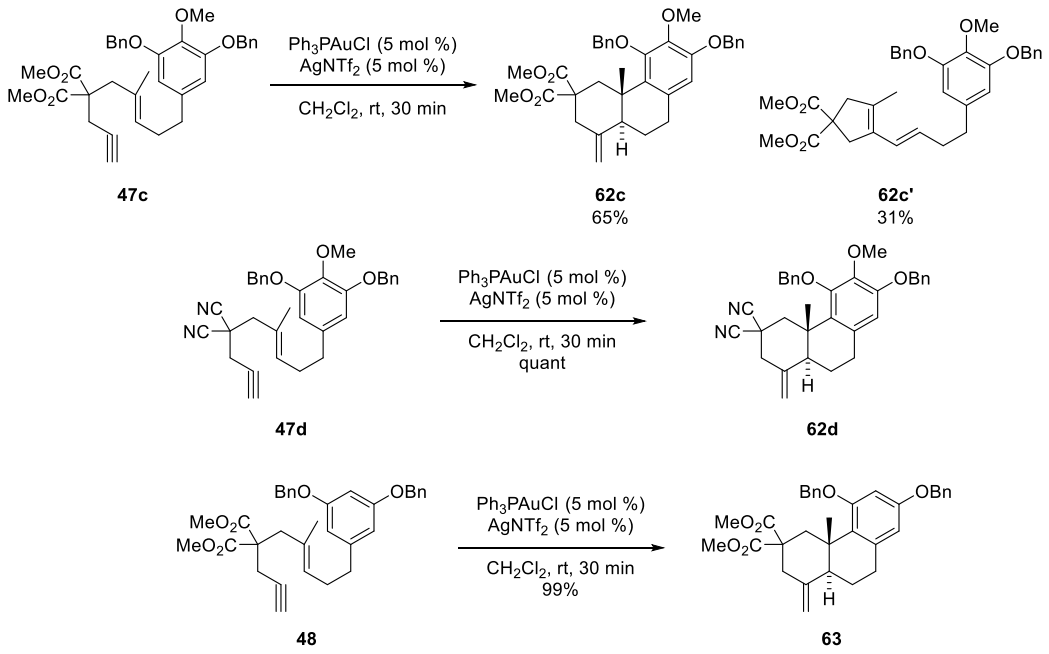
Scheme 3.18. Preparation of Substrate **48**



Reagents and Conditions: (a) **58**, Mg, $(CH_2Br)_2$, Li_2CuCl_4, THF, 0 °C, 1 h; (b) TBAF, THF, rt, 30 min, 96% (2 steps); (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, 88%; (d) dimethyl malonate, NaH, THF, rt, 12 h, quant; (e) propargyl bromide, NaH, THF, rt, 4 h, 96%.

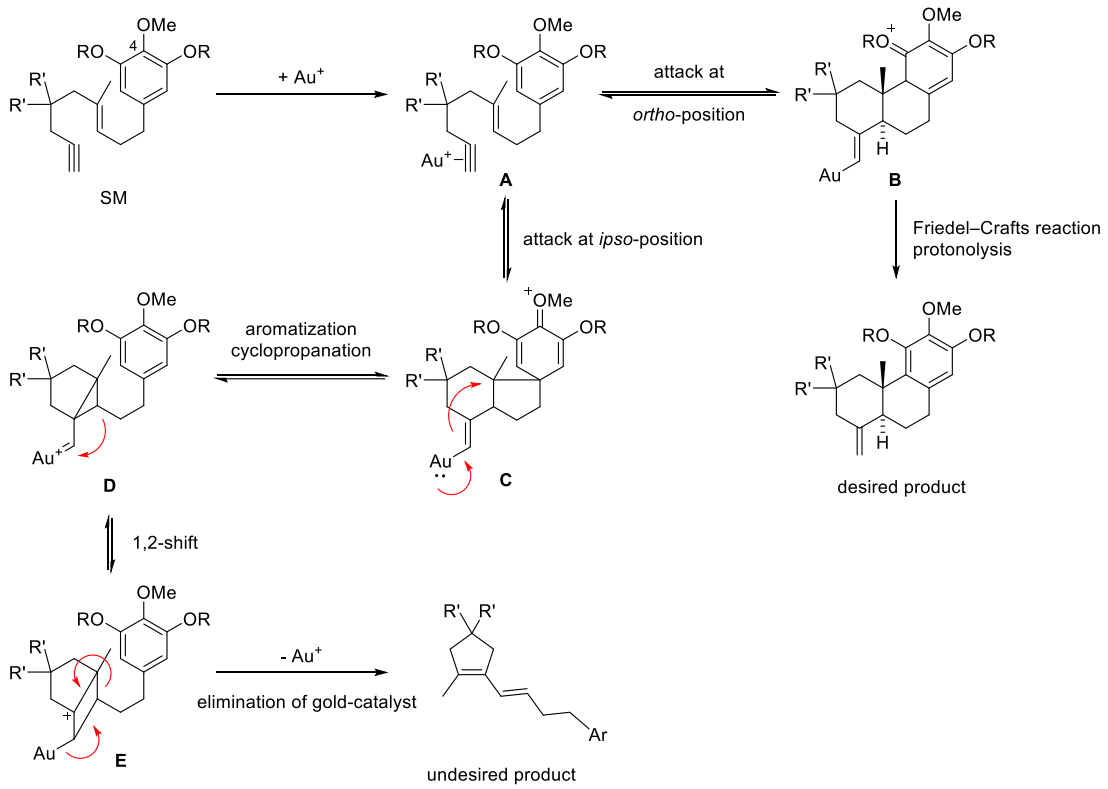
合成した環化基質を用いて 1,6-エンイン環化異性化を行った(Scheme 3.19)。エステル部位を有する基質 **47c** を用いた場合、目的生成物 **62c** が 65%、5 員環化合物 **62c'**が 31%得られた。目的生成物の収率は向上したため、反応点の増加の影響は見られたものの、依然として **62c'**の生成の抑制には至らなかった。また、シアノ基を有する基質 **47d** を用いた反応では、選択的に目的生成物 **62d** が得られた。一方、環化基質 **48** を用いると、エステルを有しているが、選択的に目的生成物 **63** が得られた。

Scheme 3.19. Gold(I)-Catalyzed Cycloisomerization of **47c,d** and **48**



以上の結果から、環化異性化には反応停止部位となる芳香環が「C4 位に電子供与基を有するか否か」が重要であると示唆された。そこで、環化異性化の反応機構を考察した(Scheme 3.20)。活性化されたアルキン **A** に対し、C3 位および C5 位の電子供与性基が働き、環化が進行すると **B** を経由して、目的生成物を得ることができる。しかし、4 位の電子供与性基が作用すると、イプソ位で環化が進行し、**C** が生成する。続けて芳香環化を伴い、シクロプロパン **D** が生成すると考えられる。エステルを有する基質の場合、シクロプロパン **D** はひずみの大きさから環拡大し **E** を生成する。その後、金触媒の脱離を伴い 5 員環化合物を生成すると推測した。一方、シアノ基を有する基質においては、ひずみが小さいため環拡大が起こらず、シクロプロパンの開環を経て、目的生成物が得られると考えた。

Scheme 3.20. Plausible Mechanism of the Gold(I)-Catalyzed Cycloisomerization



以上の検討から、金触媒を用いた 1,6-エンイン環化異性化には

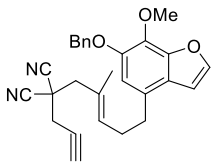
(1) Thorpe-Ingold 効果を起こす置換基

(2) 反応停止部位となる芳香環の C4 位の置換基

が多大な影響を与えることを見出した。また本反応は、非常に電子豊富な芳香環を停止部位とする初の例であり、天然物合成における骨格構築に有効な手法である。

第 3 節　エナンチオ選択的 1,6-エンイン環化異性化

目的の環化生成物を選択的に得る条件を見出したため、この環化異性化の不斉触媒化を試みた。不斉反応には、天然物合成への利用を鑑み、後に選択的に脱保護が可能であるよう、新たな基質 **64** を設定し用いた(Figure 3.3)。

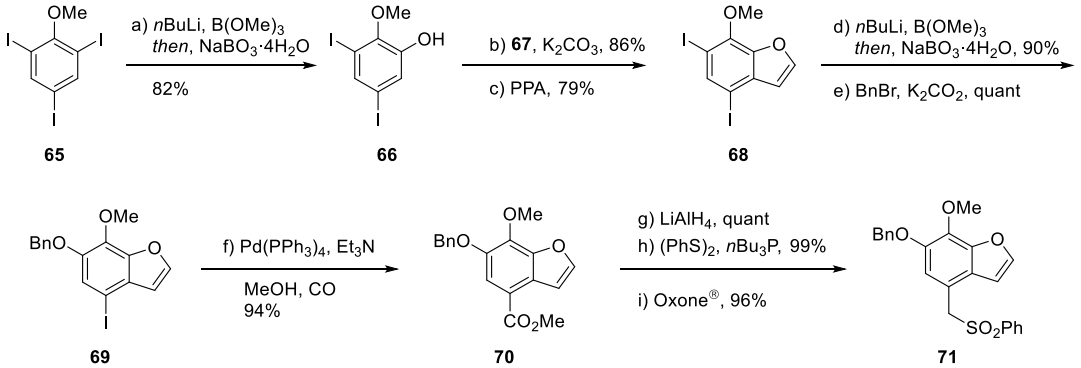


64

Figure. 3.3 Substrate of enantioselecitive 1,6-ene-yne cycloisomerization.

基質合成を以下に示す(Scheme 3.21)。2,4,6-triiodoanisole (**65**)[34] を出発原料とし、1.0 当量の *n*BuLi を作用させ、フェノール **66** を合成した[35]。続いて、bromoacetaldehyde dimethyl acetal (**67**)を用いたアルキル化、ポリりん酸による環化を行いベンゾフラン **68** へ変換した[36]。得られた **68** を再度酸化し、得られたアルコールをベンジル基で保護し、**69** を合成した。続いて、パラジウム触媒存在下、一酸化炭素挿入反応によりエステル **70** へと変換し、さらなる三工程を経て、スルホン **71** を合成した。得られたスルホン **71** を用いて、Scheme 3.17 と同様の手法で環化基質 **64** を合成した(Scheme 3.22)。

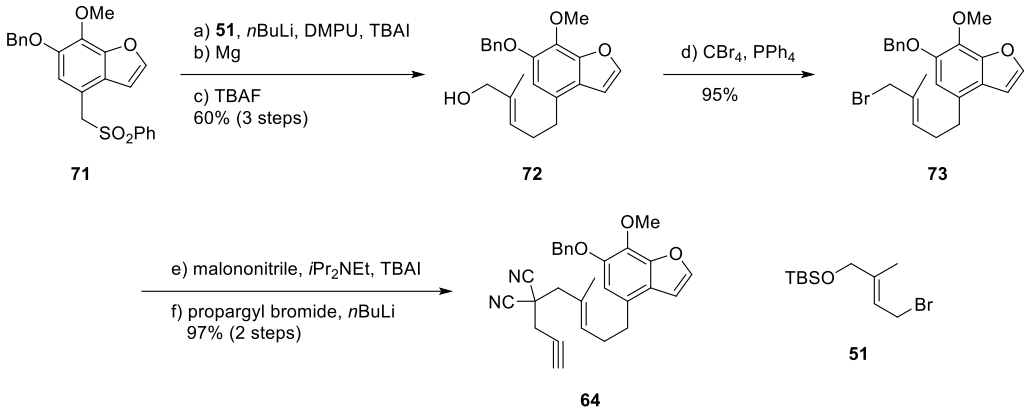
Scheme 3.21. Preparation of Sulfone **71**



65 **66** **68** **69** **70** **71**

Reagents and Conditions: (a) *n*BuLi, THF, –78 °C, 0.5 h; $B(OMe)_3$, 0 °C, 0.5 h; $NaBO_3{\cdot}4H_2O$, rt, 16 h, 99%; (b) **67**, K_2CO_3, DMF, 100 °C, 4 h, 86%; (c) polyphosphoric acid, PhMe, 100 °C, 2 h, 79%; (d) *n*BuLi, THF, –78 °C, 0.5 h; $B(OMe)_3$, 0 °C, 0.5 h; $NaBO_3{\cdot}4H_2O$, rt, 16 h, 90%; (e) BnBr, K_2CO_3, acetone, reflux, 4 h, quant; (f) $Pd(PPh_3)_4$, Et_3N, CO (g), MeOH, 50 °C, 12 h, 94%; (g) $LiAlH_4$, THF, 0 °C, 1 h, quant; (h) diphenyl disulfide, tri-*n*-butylphoshine, THF, rt, 2 h, 99%; (i) Oxone®, THF/MeOH/H_2O, 0 °C, 1 h, 96%.

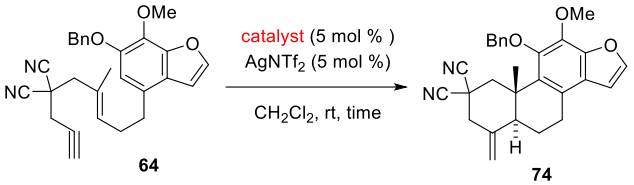
Scheme 3.22. Preparation of Substrate **64**

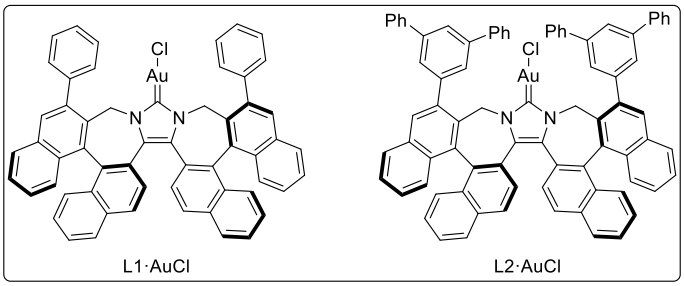


Reagents and Conditions: (a) **51**, *n*BuLi, DMPU, TBAI, THF, rt, 16 h; (b) Mg, MeOH, rt, 4 h; (c) TBAF, THF, rt, 1 h, 60% (3 steps); (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 95%; (e) malononitrile, *i*Pr_2NEt, TBAI, CH_2Cl_2, rt, 24 h; (f) propargyl bromide, *n*BuLi, THF, rt, 2 h, 97%.

合成した環化基質 **64** を用いて不斉 1,6-エンイン環化異性化の検討を行った。まず、塩化メチレン溶媒中、silver bis(trifluoromethanesulfonylimide)を用いて、金触媒の最適化を行った。まず、(*S*)-BINAP を配位子とする金二核錯体を用いた。その際、Toste らの報告を参考に、モノカチオン錯体を調製し、反応を行った[37]。その結果、1 時間で完結し、86%と高収率であったが、エナンチオ過剰率は 18%であった(entry 1)。エナンチオ過剰率の向上を狙い、種々のビナフチル配位子を用いて、反応を行ったが、エナンチオ過剰率は最高でも 29%に留まった(entries 2-6)。そこで、当研究室で開発した *N*-ヘテロ環状カルベン配位子の金錯体 L1·AuCl[38] を用いたところ、反応時間は 8 時間と長くかかったが、48% ee を示した(entry 7)。L1 の剛直な骨格がつくる不斉環境が、嵩の小さなシアノ基に対しても、有効に作用したものと考えられる。そこで、さらなるエナンチオ選択性向上のため、L1 のフェニル基を、より嵩高い 3,5-ジフェニルフェニル基に置き換えた L2 の金錯体を合成し、検討に用いた(entry 8)。その結果、エナンチオ選択性は逆転するものの、56%に向上したため、L2·AuCl を最適触媒とし、さらなる検討を続けた。

Table 3.1. Catalytic Enantioselective Gold(I)-Catalyzed Cycloisomerization of **64**



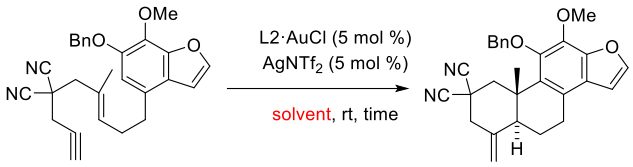


entry	catalyst	time (h)	yield (%)	ee (%)[a]
1	(*S*)-BINAP(AuCl)$_2$	1	86	18
2	(*R*)-tol-BINAP(AuCl)$_2$	1	86	–23
3	(*S*)-SEGPHOS(AuCl)$_2$	1	92	16
4	(*S*)-DTBM-SEGPHOS(AuCl)$_2$	1	85	–29
5	(*S*)-MeO-BIPHEP(AuCl)$_2$	1	92	8
6	(*S*)-MeO-DTB-BIPHEP(AuCl)$_2$	1	94	22
7	L1·AuCl	8	98	–48
8	L2·AuCl	8	87	56

[a]A minus sign "–" means reversal of the enantioselectivity.

続いて、溶媒の最適化を行った(Table 3.2)。エーテル系溶媒を用いた場合、エナンチオ選択性は低下した(entries 2,3)。一方、強い配位性溶媒アセトニトリルを用いた場合には、反応が全く進行しなかった(entry 4)。そこで、芳香族系溶媒であるベンゼンを用いると、反応時間は 3 時間に短縮されたが、エナンチオ選択性は 43%に低下した(entry 5)。興味深いことに、原因は不明であるが、ベンゼン溶媒で得られる主生成物は、塩化メチレン溶媒で得られる化合物のエナンチオマーであった。ベンゼン溶媒では良い結果が得られなかったものの、さらに芳香族系溶媒の検討を行った。トルエンを用いると、53% ee に向上した(entry 6)。さらにメチル基の増加したキシレンを用いて反応を行ったところ、*m*-キシレン溶媒のとき、68% ee と最も高い結果を与えた(entries 7-9)。メチル基を 3 つ持つメシチレンを溶媒としても、さらなるエナンチオ選択性の向上は見られなかった(entry 10)。一方で、電子不足なクロロベンゼンを用いるとエナンチオ選択性は低下した(entry 11)。以上の結果から、*m*-xylene を用いた時、最高のエナンチオ選択性を与えたため、最適溶媒とした。

Table 3.2. Catalytic Enantioselective Gold(I)-Catalyzed Cycloisomerization of **64**



64 **74**

entry	solvent	time (h)	yield (%)	ee (%)[a]
1	CH_2Cl_2	8	87	56
2	THF	3	68	39
3	Et_2O	71	57	–47
4	MeCN	-	NR	-
5	benzene	3.5	87	–43
6	toluene	3	92	–53
7	*o*-xylene	3	91	–53
8	*m*-xylene	2.5	87	–68
9	*p*-xylene	4	91	–63
10	mesitylene	4.5	81	–66
11	PhCl	1.5	92	–33

[a]A minus sign "–" means reversal of the enantioselectivity.

最後に銀塩の検討を行い、$AgBF_4$ を用いたとき、85% ee という最高の結果が得られた (Table 3.3, entry 4)。しかし、原料が消失せず、収率は 41%に留まった。

Table 3.3. Catalytic Enantioselective Gold(I)-Catalyzed Cycloisomerization of **64**

64 **74**

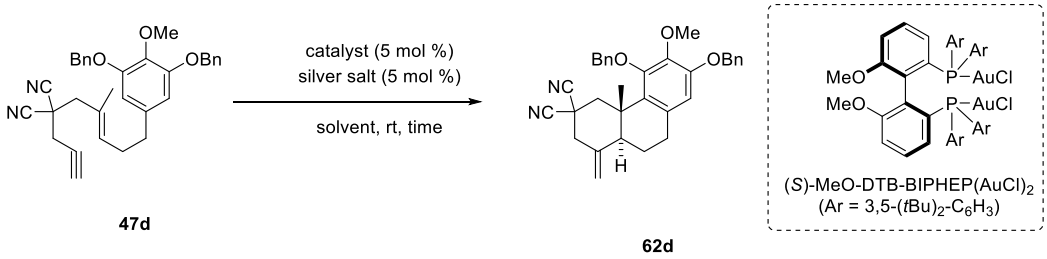
entry	silver salt	time (h)	**64** (%)	**74** (%)	ee (%)[a]
1	$AgNTf_2$	2.5	0	87	–68
2	$AgPF_6$	93	72	23	–62
3	$AgSbF_6$	7	0	95	–64
4	AgOTf	24	21	71	–78
5	$AgBF_4$	46	46	41	–85
6	NaBArF	70	0	94	25

[a]A minus sign "–" means reversal of the enantioselectivity.

ベンゾフランを有する基質 **64** を用いた環化異性化において高いエナンチオ選択性を示す条件を見出したため、3,5-dibenzyloxy-4-methoxyphenyl 基を反応停止部位とする基質 **47d** の触媒的不斉環化異性化も検討を行った(Table 3.4)。

その結果、この基質においては、(*S*)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl を配位子とするカチオン性金錯体が有効であった(enties 1-3)。また、溶媒は *p*-キシレンを用いたとき、最も高いエナンチオ選択性を示した(entries 4 and 5)。Entries 6-9 では銀塩の検討を行い、その結果 AgOTf が最適であり、収率 92%、73% ee で生成物を得た。これまでの検討から反応停止部位の芳香環が環化反応に与える影響が大きいことが示唆されたため、大きな立体障害によりエナンチオ選択性が向上することを期待し、ベンジル基より嵩高いトリイソプロピルシリル基を持つ基質 **78** を合成した(Scheme 3.23)。**78** を反応に用いた結果、収率 94%、86% ee に向上した(Scheme 3.24)。

Table 3.4. Catalytic Enantioselective Gold(I)-Catalyzed Cycloisomerization of **47d**

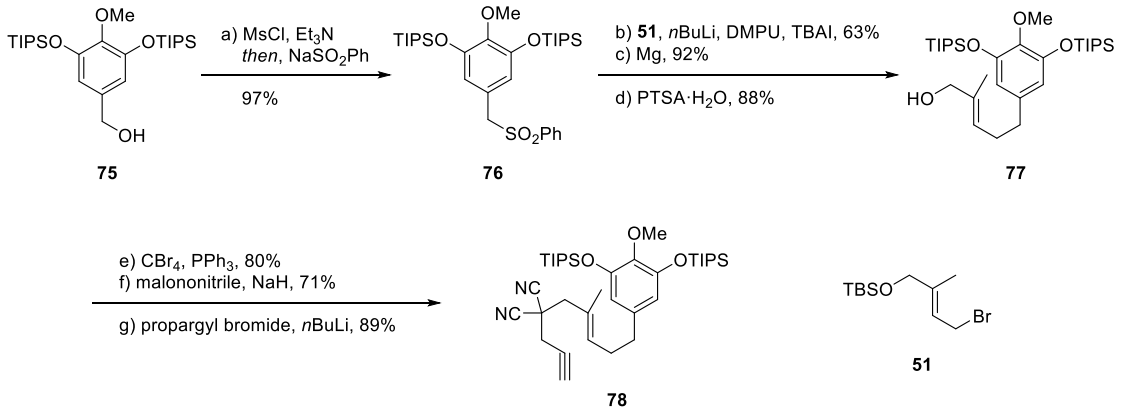


47d **62d**

entry	catalyst	silver salt	solvent	time (h)	yield (%)	ee (%)[a]
1	L2·AuCl	$AgNTf_2$	*m*-xylene	3	94	–40
2	(*S*)-DTBM-SEGPHOS$(AuCl)_2$	$AgNTf_2$	*m*-xylene	1	92	–45
3	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgNTf_2$	*m*-xylene	1	99	65
4	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgNTf_2$	*o*-xylene	1	97	60
5	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgNTf_2$	*p*-xylene	1	95	67
6	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgSbF_6$	*p*-xylene	1	99	46
7	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgPF_6$	*p*-xylene	64	71 (SM:28%)	61
8	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	$AgBF_4$	*p*-xylene	3	87	70
9	(*S*)-MeO-DTB-BIPHEP$(AuCl)_2$	AgOTf	*p*-xylene	7	92	73

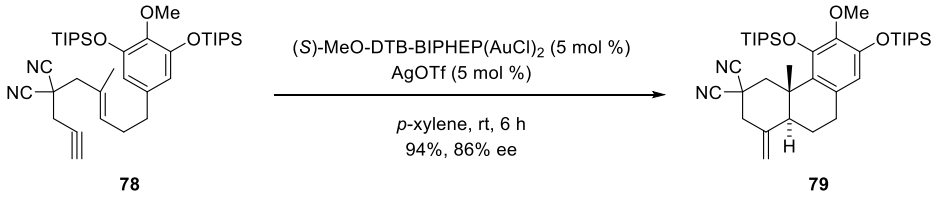
[a]A minus sign "–" means reversal of the enantioselectivity.

Scheme 3.23. Preparation of Substrate **78**



Reagents and Conditions: (a) MsCl, Et_3N, DMF, 0 °C, 0.5 h; $NaSO_2Ph$, rt, 4 h, 97%; (b) **51**, *n*BuLi, DMPU, TBAI, THF, rt, 16 h, 63%; (c) Mg, MeOH, rt, 4 h, 92%; (d) PTSA·H_2O, THF/H_2O, rt, 2 h, 86%; (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h, 80%, (f) malononitrile, NaH, THF, rt, 24 h, 71%; (g) propargyl bromide, *n*BuLi, THF, rt, 2 h, 89%.

Scheme 3.24. Catalytic Enantioselective Gold(I)-Catalyzed Cycloisomerization of **78**



以上より、第 2 節で合成した三環式化合物のエナンチオ選択的な 1,6-エンイン環化異性化への応用に成功した。選択的な 6-*exo-dig* 型の環化に必要なシアノ基は立体障害の小さな置換基であるが、高エナンチオ選択性を示す条件を見出した。ベンゾフランを有する基質 **64** を用いた反応では当研究室で開発した L2·AuCl が最適であり、5 員環形成反応においてのみ検討を行った本錯体が、6 員環形成反応においても効果的であることが確認された。本反応により得られる高度に酸化された三環式化合物は天然物の不斉全合成に応用可能である。

第 4 章　bruceantin の不斉全合成研究

第 1 節　研究背景

bruceantin (**80**)は、エチオピア産ニガキ科植物 *Brucea antidysenterica* の樹皮から得られる苦み成分 quassinoid の一つであり、1972 年に Kupchan らによって単離・構造決定が成された化合物である(Figure 4.1)[39]。

ニガキ科植物は世界各地で伝承医薬として知られ、古くから腫瘍やマラリア・胃炎などの治療に用いられてきた。特に bruceantin は扁平上皮がんや前立腺がんをはじめとする各種腫瘍細胞に対する強い増殖阻害活性を示すことが、研究により明らかとなった [40]。また、動物実験においては抗がん作用も確認されている。1980 年代には抗がん剤として臨床試験が行われたが、薬効性の低さから Phase III には至らなかった。加えて天然から得難いため、構造活性相関研究が滞っているのも現状である。しかしながら、今後、供給量が増加し、構造活性相関研究が進展するのであれば、抗腫瘍性抗生物質としての可能性が期待される。

bruceantin は、10 の不斉中心を有するトリテルペノイドである。構造的特徴として、AB 環及び BC 環に連続した *trans* 縮環部位をもつこと、D 環はラクトン、E 環はテトラヒドロフランであることが挙げられる。特に C 環は高度に酸化されており、複雑な立体化学と併せて、全合成の標的化合物として注目を集めてきた。しかし、多くの研究者が合成研究を報告しているものの、全合成の達成は村江らの形式合成及び不斉全合成 [41]、Grieco らのラセミ体での全合成 [42] の 3 例に留まる。しかし、村江らの不斉合成はリレー合成であり、いずれも工程数が多いため、大量供給に耐えうるものではない。

以上の背景から、私は quassinoid 骨格の効率的不斉構築法の確立と bruceantin の短工程での不斉全合成を目的として、研究に着手した。

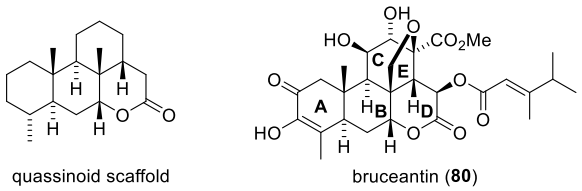


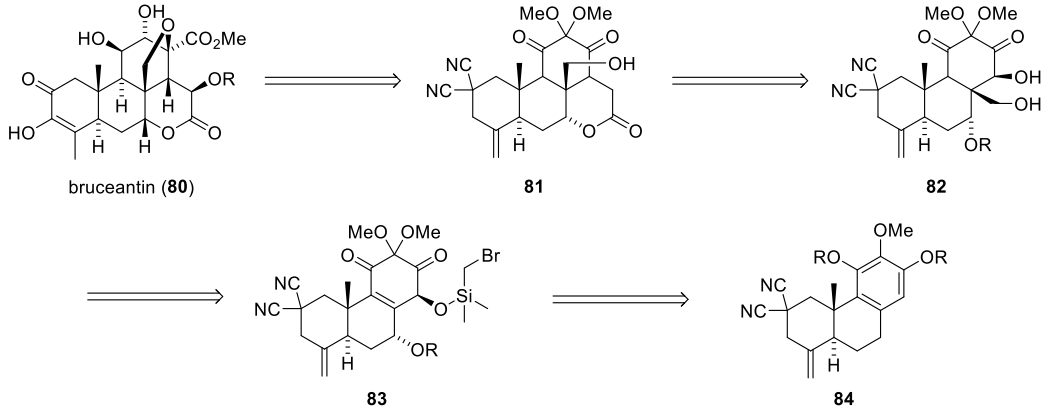
Figure 4.1. Structure of bruceantin (**80**).

第 2 節　bruceantin の CDE 環部位の構築検討

第 3 章に記載した 1,6-エンイン環化異性化により得られる三環式骨格は *trans* 縮環を持ち、高度に酸化された骨格を有するために、bruceantin の全合成へ利用可能であると考えた。不斉 1,6-エンイン環化異性化において、収率、エナンチオ選択性共に良好であった **62d** および **79** を出発原料とした。

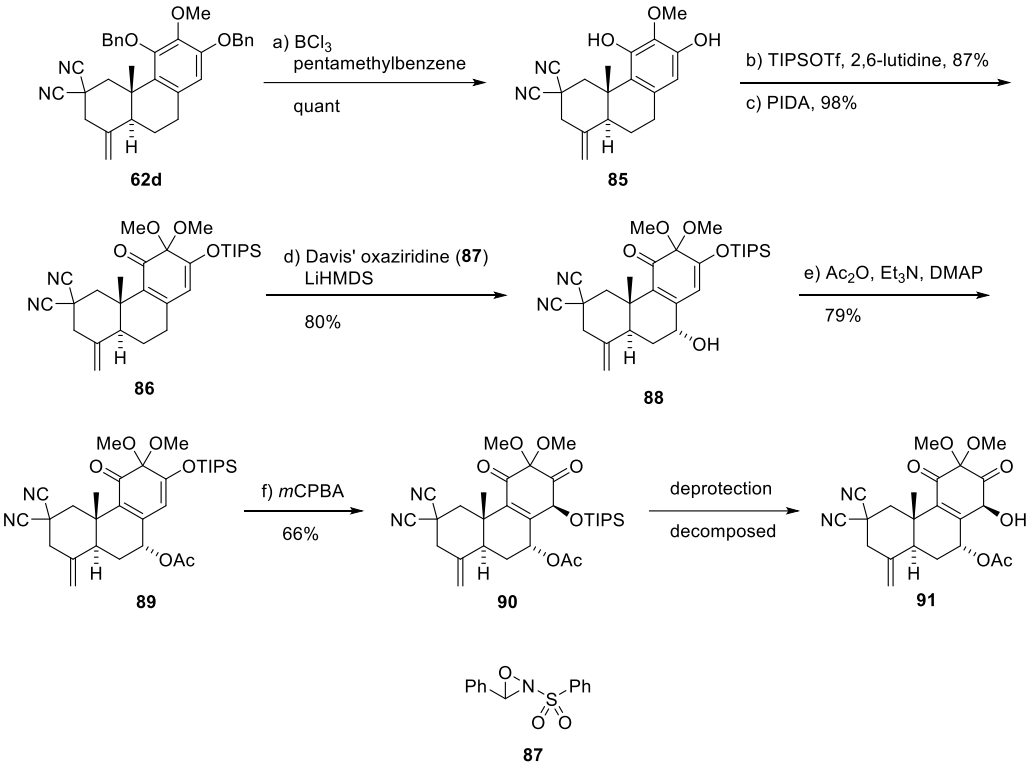
三環式化合物 **84** (R = Bn, TIPS)を用いた、bruceantin の CDE 環の合成計画を Scheme 4.1 に示す。bruceantin (**80)**は四環式化合物 **81** からテトラヒドロフラン環の構築および官能基変換により得られるものと考えた。また、**81** は **82** の α-ヒドロキシケトンを脱離基へ変換した後、エステルの環化反応による合成を計画した。そのジオールはブロモメチルシリル基のラジカル環化、続く Tamao-Fleming 酸化により得られると考えた。**83** は三環式化合物 **84** の官能基変換と Rubottom 酸化により構築できるものとして、合成に取り掛かった。

Scheme 4.1. Retrosynthetic Analysis of Bruceantin (**80**)



ラジカル環化を行う基質の合成検討を Scheme 4.2 に示す。まず、三塩化ホウ素を過剰量のカチオン捕捉剤存在下に作用させることで、二つのベンジル基の脱保護を行い、**85** を合成した [43]。得られたアルコールのトリイソプロピルシリル基による保護は、立体障害の影響を受け、選択的に進行した。続けて酸化的脱芳香環化を行い、**86** を合成した。得られたエノン **86** のγ位の Davis' oxaziridine (**87**)によるヒドロキシル化は、塩基に LiHMDS を用いることで選択的に進行し、得られたアルコールはアセチル基で保護し、**89** を合成した。**89** のシリルエノールエーテル部位に対し、*m*CPBA を用いた Rubottom 酸化を行ったところ、速やかに反応は進行し、立体選択的に α-シロキシケトン **90** を得ることに成功した。しかし、このトリイソプロピルシリル基の脱保護は、種々の条件を用いて行ったが、複数の化合物が生成し、目的のアルコール **91** を得ることが出来なかった。そのため、この合成ルートは断念した。

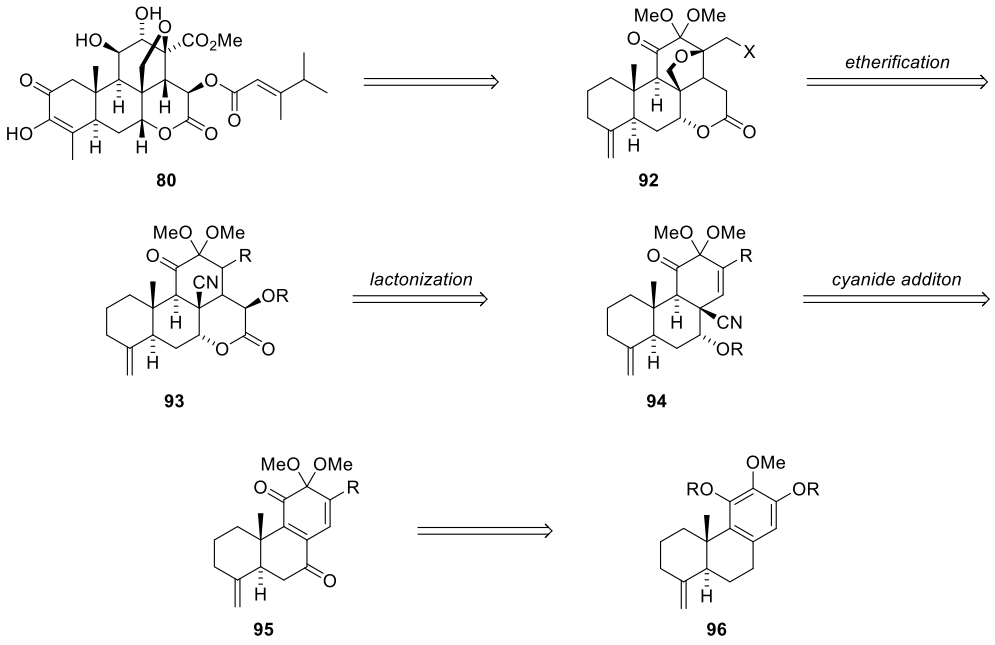
Scheme 4.2. Attempted Preparation of Cyclization Precursor



Reagents and Conditions: (a) BCl_3, pentamethylbenzene, CH_2Cl_2, 0 °C, 3 h, quant; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 12 h, 87%; (c) PIDA, MeOH, 0 °C, 2 h, 98%; (d) LiHMDS, THF, –78 °C, 30 min; Davis' oxaziridine **87**, 0 °C, 2 h, 80%; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 3 h, 79%; (f) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h, 66%.

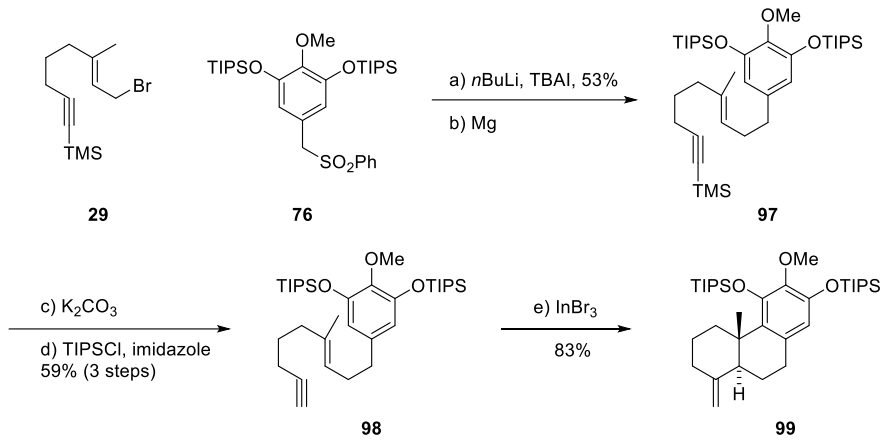
目的とした化合物 **91** の有するビニロガス活性メチン部位の不安定性が原因であると考え、新たな合成経路を計画した。その際、A 環のビスニトリル部位は反応性が高いため、CDE 環の構築に先んじて変換する必要があると考えた。したがって、A 環部位にエキソメチレン以外の官能基を持たない **96** を CDE 環構築検討のモデル基質として設定した。その合成計画を Scheme 4.3 に示す。CDE 環を構築した化合物 **92** は、ニトリル **93** の還元とエーテル環形成により得られると考えた。**93** はエステル **94** の環化により得られ、**94** はシアン化物イオンの 1,4-付加により得られるとした。α,β,γ,δ-不飽和ケトン **95** は、**96** の 1,6-エンイン環化異性化の反応停止部位として利用した芳香環の変換により得られるとした。

Scheme 4.3. Retrosynthetic Analysis of Bruceantin(**80**)



まず、不斉 1,6-エンイン環化異性化反応で最高の結果を与えたトリイソプロピルシリル基を芳香環に持ち、A 環部位のシアノ基を除去した三環式化合物 **99** をモデル化合物として設定し、合成を行った(Scheme 4.4)。スルホン **76** を臭化物 **29** と反応させ、アルキル化した。続いて、マグネシウムを用いた一電子還元を行い、脱スルホン化し **97** を合成した。得られた **97** にメタノール溶媒中、炭酸カリウムを作用させトリメチルシリル基の脱保護を行ったが、一部トリイソプロピルシリル基の脱保護が確認されたた。そのため、後処理後、単離精製を行わずに、再度保護し、環化基質 **98** を得た。**98** に対して、臭化インジウムを用いて 1,6-エンイン環化異性化を行うことで、三環式化合物 **99** の合成に成功した。

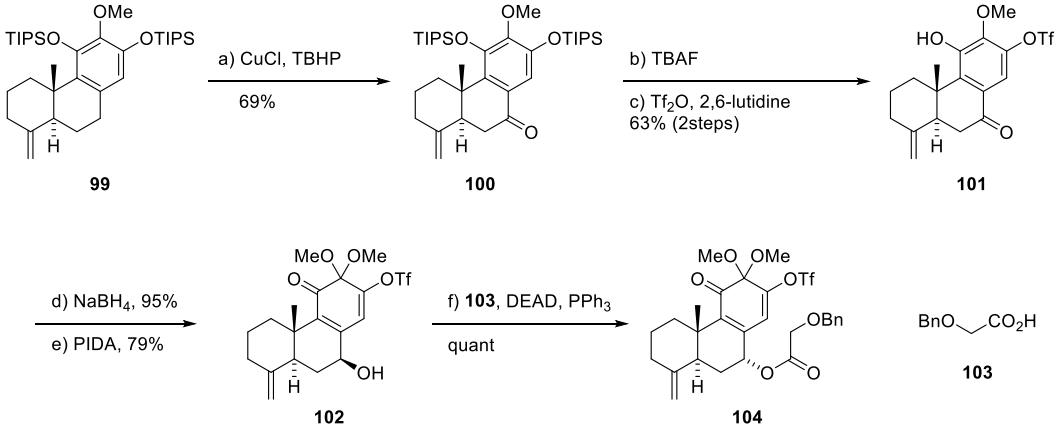
Scheme 4.4. Preparation of **99**



Reagents and Conditions: (a) *n*BuLi, TBAI, THF/DMPU, 0 °C, 30 min; **29**, rt, 16 h, 53%; (b) Mg, MeOH, rt, 16 h; (c) K_2CO_3, MeOH, rt, 1 h; (d) TIPSCl, imidazole, rt, 12 h, 59% (3 steps); (e) $InBr_3$, CH_2Cl_2, –20 °C, 3 h, 83%.

三環式化合物 **99** が得られたため、合成計画に基づき、α,β,γ,δ-不飽和ケトンの合成に着手した。**99** に対し、銅触媒を用いたベンジル位酸化を行い、**100** を合成した(Scheme 4.5)[44]。続いて、二つのトリイソプロピルシリル基を脱保護し、選択的にトリフルオロメタンスルホニル基を導入した。その後、ケトンの立体選択的還元、酸化的脱芳香環化を行い、α,β,γ,δ-不飽和ケトン **102** へと変換した。**102** のアルコールを、カルボン酸 **103**[45] を用いた光延反応により **104** へ変換した。

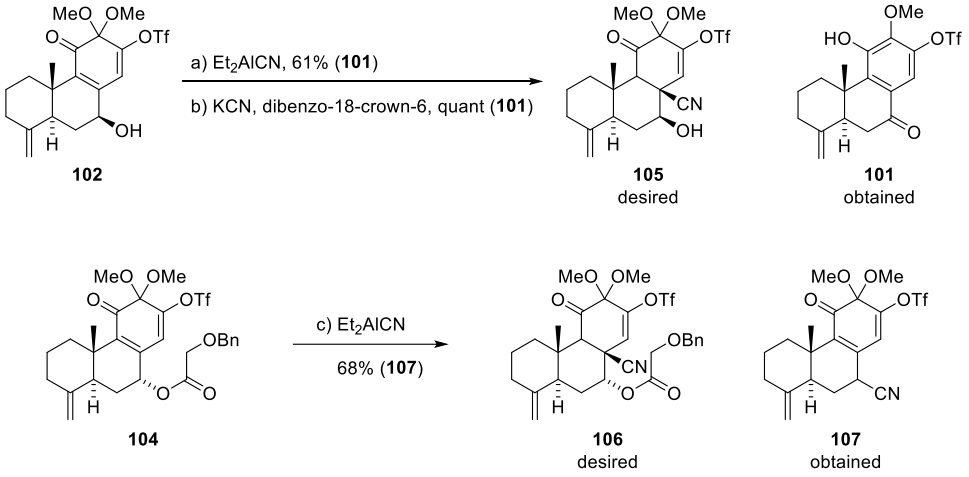
Scheme 4.5. Preparation of α,β,γ,δ-Unsaturated Ketone **104**



Reagents and Conditions: (a) CuCl, TBHP in decane, *t*BuOH, 50 °C, 24 h, 69%; (b) TBAF, THF, rt, 30 min; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 63% (2 steps); (d) $NaBH_4$, MeOH, 0 °C, 1 h, 95%; (e) PIDA, MeOH, 0 °C, 1 h, 79%; (f) **103**, DEAD, PPh_3, THF, rt, 1 h, quant.

得られた α,β,γ,δ-不飽和ケトン **102**、**104** に対して、永田試薬やシアン化カリウムを用いて、シアニドの付加を行った(Scheme 4.6)。しかし、目的とする 1,4-付加体 **105**、**106** は得られず、芳香族化した **101** や、エステル部位がシアノ基に置換した **107** が得られた(Scheme 4.6)。**102** との反応は、シアニドの求核付加反応は 1,2-付加と 1,4-付加が競合する反応であるため、1,2-付加が起きた際に、芳香環化が進行し、**101** が生成したものと考えられる。**104** との反応は、立体障害の小さな位置に存在するエステルがルイス酸により活性化され、シアニドと置換したものと考えている。

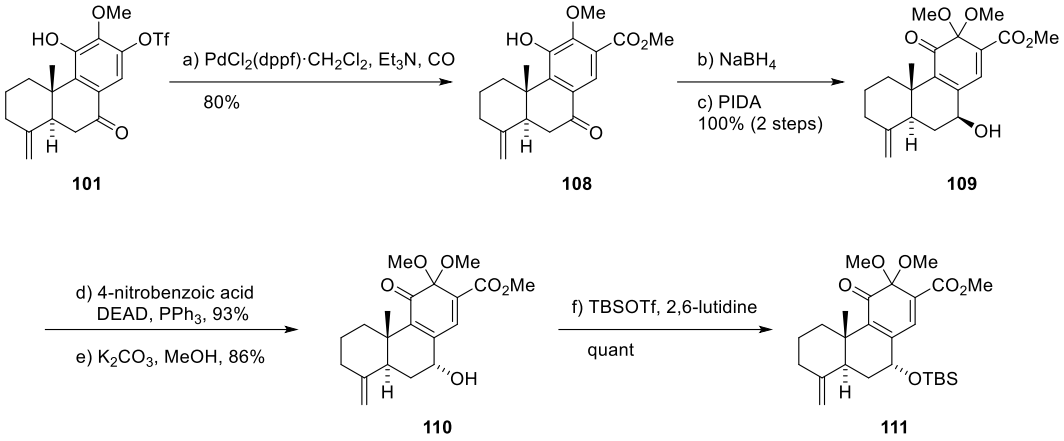
Scheme 4.6. Attempted Cyanide Addition of **102** and **104**



Reagents and Conditions: (a) Et_2AlCN, PhMe, rt to 50 °C, 12 h to 12 h; 61% (**101**); (b) KCN, dibenzo-18-crown-6, PhMe, rt, 14 h, quant (**101**); (c) Et_2AlCN, PhMe, rt, 8 h, 68% (**107**).

そこで、α,β,γ,δ-不飽和ケトンの電子密度をさらに低下させ、反応性が上がるようメトキシカルボニル基の導入を行った。トリフラート **101** に対し一酸化炭素挿入反応を行い、エステル **108** を合成した(Scheme 4.7)。その後、同様の変換により、α,β,γ,δ-不飽和ケトン **109** を合成した。光延反応および加メタノール分解により、立体反転したアルコール **110** を合成し、TBS 基で保護し、**111** を得た。

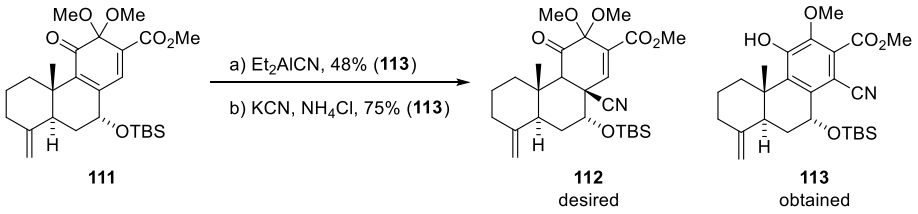
Scheme 4.7. Preparation of α,β,γ,δ-Unsaturated Ketone **111**



Reagents and Conditions: (a) $PdCl_2(dppf)\cdot CH_2Cl_2$, Et_3N, CO (g), MeOH, reflux, 12 h, 80%; (b) $NaBH_4$, MeOH, 0 °C, 1 h; (c) PIDA, MeOH, 0 °C, 1 h, 100% (2 steps); (d) 4-nitrobenzoic acid, DEAD, PPh_3, THF, 0 °C, 1 h, 93%; (e) K_2CO_3, MeOH, 0 °C, 1 h, 86%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, quant.

エノン **111** に対するシアニドの付加反応を行ったが、立体障害の大きなケトンの β 位を避け、エステルの β 位から 1,4-付加した後、芳香環化まで進行した **113** が得られた(Scheme 4.8)。

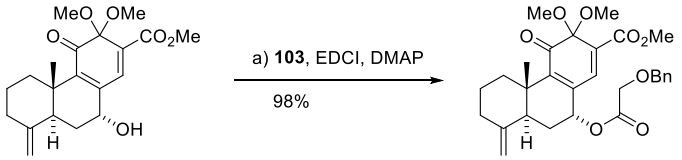
Scheme 4.8. Attempted Cyanide Addition of **111**



Reagents and Conditions: (a) Et_2AlCN, PhMe, 80 °C, 36 h, 48% (**113**); (b) KCN, NH_4Cl, DMF/H_2O, 80 °C, 12 h, 75% (**113**).

Scheme 4.8 の検討から、ケトンに比べエステルの方が、反応性が高いことが示唆されため、ラクトン環を先に構築し、次いで 4 級立体中心を導入する経路を採ることにした。アルコール **110** とカルボン酸 **103** との脱水縮合を行い、エステル **114** を合成し、反応基質とした(Scheme 4.9)。

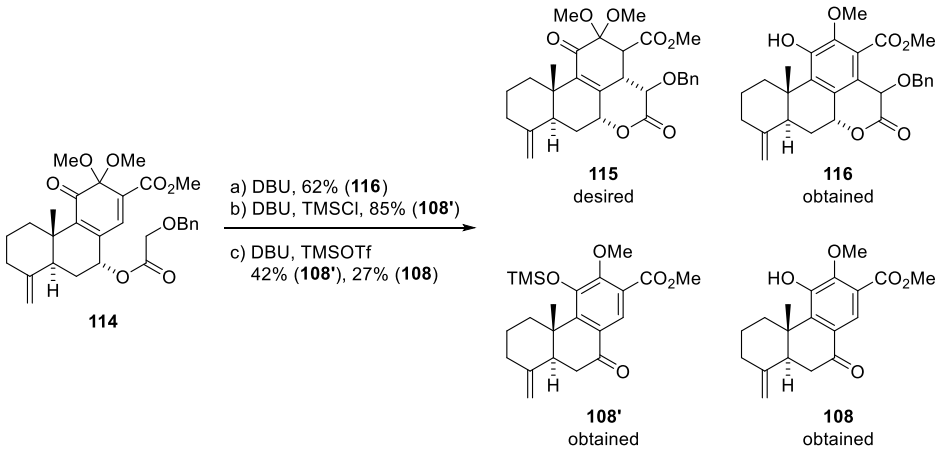
Scheme 4.9. Preparation of Ester **114**



Reagents and Conditions: (a) **103**, EDCI, DMAP, THF, rt, 1 h, 98%.

得られたエステル **114** に対し DBU を作用させ、ラクトン環の構築を行った(Scheme 4.10)。その結果、ラクトン環の構築は進行したが、エノラートを経由したメトキシ基の β 脱離と芳香環化が進行した **116** が得られた。また、エノラートを捕捉し、メトキシ基の脱離を抑制するため、シリル化剤(TMSCl、TMSOTf)を添加し、反応を行った。しかし、**116** は痕跡量確認されるのみであり、エステルが分解した **108** や **108'**が主生成物であった。これらの試薬がルイス酸としての作用を示すためであると思われる。

Scheme 4.10. Attempted Cyclization of **114**

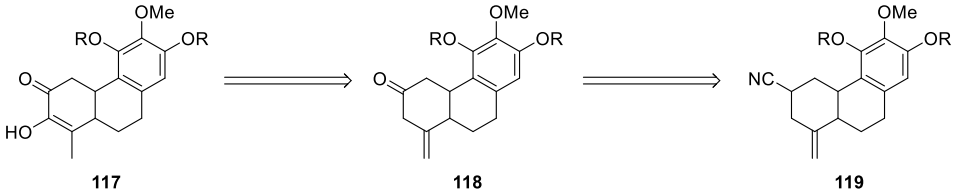


Reagents and Conditions: (a) DBU, PhMe, 50 °C, 2 h, 62% (**116**); (b) DBU, TMSCl, THF, rt, 16 h, 85% (**108'**); (c) DBU, TMSOTf, THF, rt, 16 h, 42% (**108'**), 27% (**108**).

第 3 節　bruceantin の不斉全合成を志向した A 環部位の構築

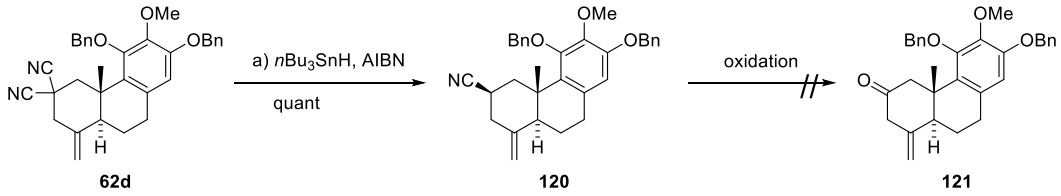
第 3 章に記載した触媒的不斉環化異性化により得られる三環式化合物を用いた、bruceantin の不斉全合成へ向けた変換も検討を行った。立体選択的な環化異性化に必要であったシアノ基のうち一つを還元により除去した **118** を合成し、続いて酸化反応を行うことで bruceantin の構造に対応するよう官能基変換を行うことを計画した(Scheme 4.11)。

Scheme 4.11. Synthetic Plan of A-Ring Moiety



まず、ラジカル還元反応により **62d** のシアノ基を一つ除去し、**120** を合成した[46]。続けて、シアノ基を酸化し、シアノヒドリンを経由するケトン **121** の合成を試みた(Scheme 4.12)。しかし、酸化はいずれの条件(base + Davis' oxaziridine, O_2, MoOPh)においても進行せず、原料が回収されるのみであった。

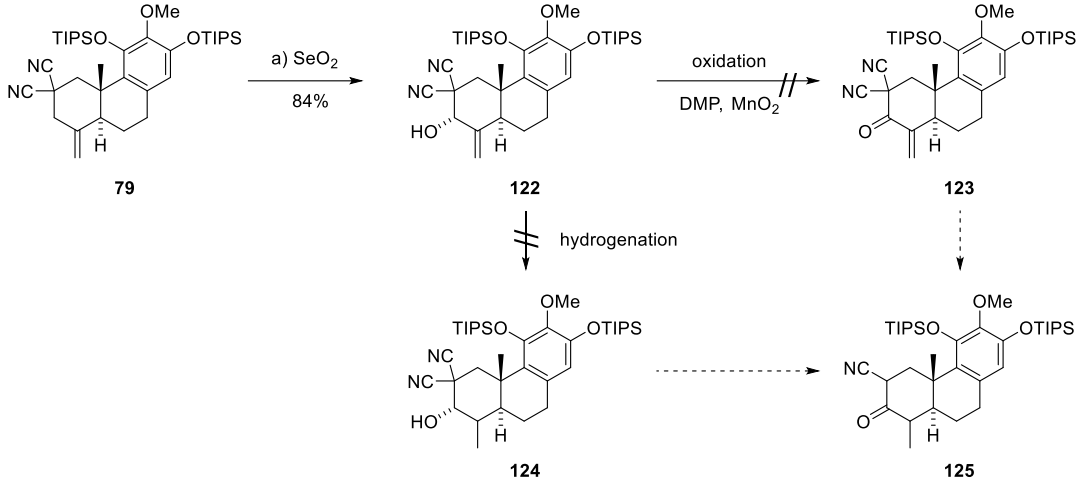
Scheme 4.12. Conversion toward A-ring Moiety of Bruceantin



Reagents and Conditions: (a) nBu$_3$SnH, AIBN, PhMe, 100 °C, 36 h, quant.

シアノ基の α 位のアニオンの生成が起きていないことが原因として考えられたため、α-シアノケトンを合成し、より酸性度の高い活性メチン部位を導入することとした(Scheme 4.13)。まず、**79** に対しアリル位酸化を行い、アルコール **122** を合成した[47]。続いて、アリルアルコールの酸化を行い、エノン **123** の合成を試みたが、不安定であり、単離困難であった。一方、接触水素化によるエキソメチレンの還元を行った場合、複数の生成物が得られたが、いずれも目的物ではなく **124** を得ることはできなかった。

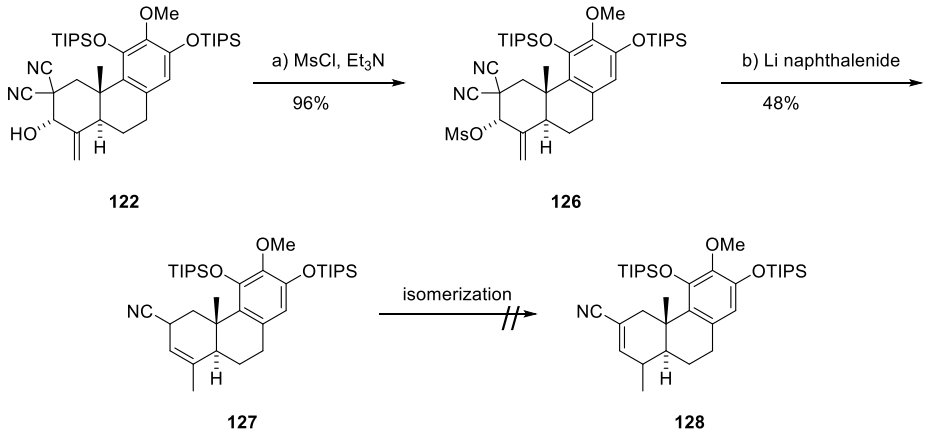
Scheme 4.13. Conversion toward A-ring Moiety of Bruceantin



Reagents and Conditions: (a) SeO_2, THF, reflux, 8 h, 84%.

続いて、ヒドロキシル基とシアノ基を還元的に除去し、得られる α,β-不飽和ニトリルのジヒドロキシル化による α-ヒドロキシケトンへの変換を計画した(Scheme 4.14)。アリルアルコール **122** にメタンスルホニルクロリドを作用させ、メシラート **126** を合成した。**126** に対してリチウムナフタレニドを用いた一電子還元を行うと、メシル基およびシアノ基が除去された化合物が得られた。^{1}H NMR による構造解析の結果、得られた化合物は β,γ-不飽和ニトリル **127** であると確認した。したがって、α,β-不飽和ニトリルへの異性化を試みた。異性化反応には塩基、遷移金属触媒を用い検討を行ったが、いずれの場合にも目的の α,β-不飽和ニトリル **128** を選択的に得ることはできず、最大でも 4:1 (**128**:**127**)の比率であった。また、**127** と **128** の分離は困難であった。

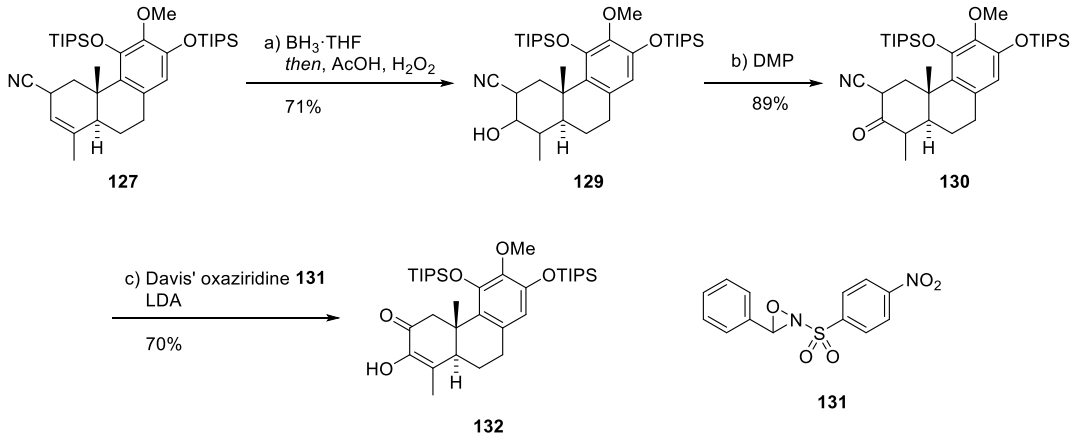
Scheme 4.14. Conversion toward A-ring Moiety of Bruceantin



Reagents and Conditions: (a) MsCl, Et_3N, CH_2Cl_2, rt, 5 h, 96%; (b) lithium naphthalenide, THF, rt, 10 min, 48%.

選択的にα,β-不飽和ニトリルを得ることが困難であったため、β,γ-不飽和ニトリルを用いて合成検討を続けた(Scheme 4.15)。まず、**127** にボランを作用させ、続く酸化によりアルコール **129** を立体選択的に合成した。**129** に対し、DMP を用いた酸化を行うことで、α-シアノケトン **130** を得ることに成功した。**130** の活性メチン部位のアニオンの発生は速やかに起こり、Davis' oxaziridine (**131**)[48] を作用させることで、シアノヒドリンが得られた。得られたシアノヒドリンは塩基性条件下、後処理を行うことで分解し、bruceantin の A 環部位に相当する **132** を合成することに成功した。**132** は bruceantin と同様に一方がエノール化していることを ^{1}H NMR 解析により確認した。

Scheme 4.15. Conversion toward A-ring Moiety of Bruceantin



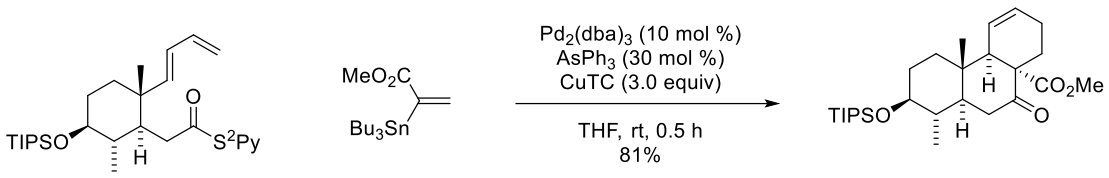
Reagents and Conditions: (a) BH_3·THF, THF, 0 °C, 3 h; AcOH, H_2O_2, rt, 16 h, 71%; (b) DMP, CH_2Cl_2, rt, 1 h, 89%; (c) **131**, LDA, –78 °C, 1 h, 70%.

得られた **132** の二つのケト基は還元によりジオールへと変換し、適切な保護基を用いることで、CDE 環の構築へ利用可能である。そして、bruceantin の不斉全合成達成へと繋ぐことを計画している。

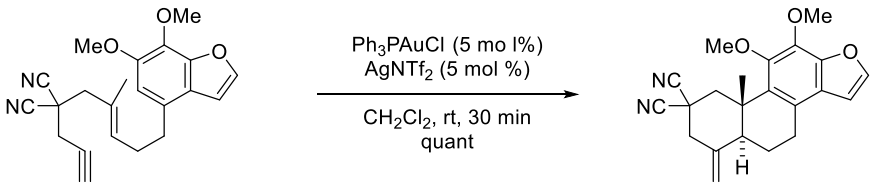
第 5 章　総括

本論文を以下に総括する。

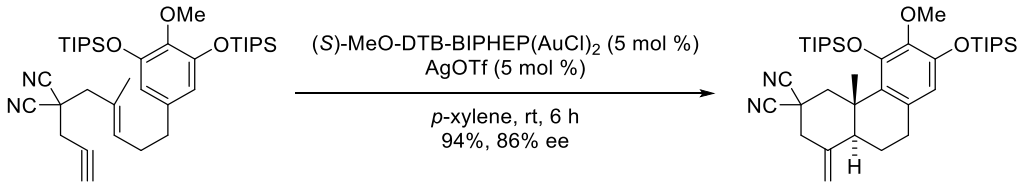
1．　Liebeskind-Srogl カップリング/分子内 Diels-Alder 連続反応を開発し、*trans-trans-cis* 縮環を持つ三環式化合物を得ることに成功した。本反応により一挙に 3 つの立体中心の構築が可能である。Liebeskind-Srogl カップリングを起点とする連続反応はこれまでに例がなく、本骨格は kauranoid などの天然物合成に展開可能である。



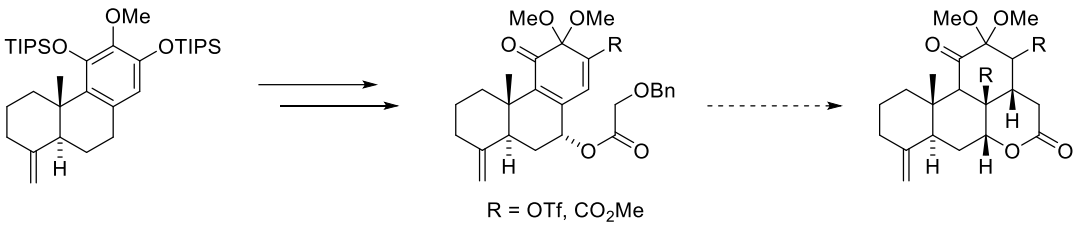
2．　1,6-エンイン環化異性化により *trans* 縮環を有する三環式化合物を合成した。Thorpe-Ingold 効果を与える置換基により、環化形式が異なることを見出した。また、ベンゾフランを反応停止部位とする初めての例を見出した。



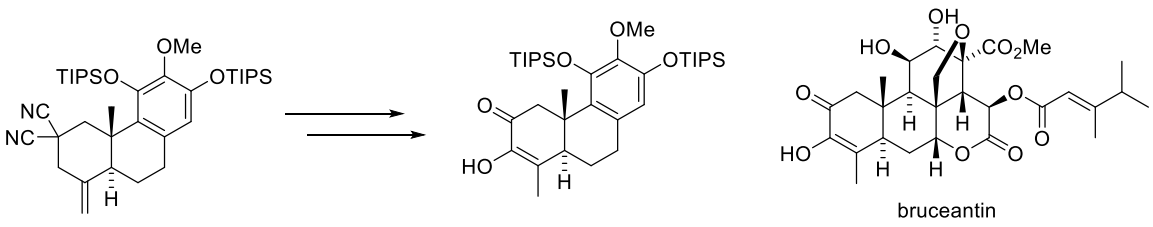
3．　不斉 1,6-エンイン環化異性化の検討により高いエナンチオ選択性を示す条件を見出した。立体障害の小さなシアノ基を有する基質での高いエナンチオ選択性の発現には、嵩高い配位子を持つ金触媒が有効であった。



４．　1,6-エンイン環化異性化により得られる三環式化合物を原料として、bruceantin の全合成研究を行った。モデル化合物を用いて、B 環に結合したエステル部位を立体選択的に構築した。



５．　不斉 1,6-エンイン環化異性化により得られるシアノ基を有する環化体に対して、変換を施し、bruceantin の A 環部位の合成に成功した。



第6章　実験項

General Information

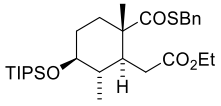
^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-500, ECZ-500 spectrometer and a BRUKER AVANCE 600 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. Chemical shift (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ (δ = 7.26 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR) as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a Thermo Fisher Scientific Inc. Nicolet 6700 FT/IR using an attenuated total reflectance (ATR) attachment. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. Melting points (mp) are uncorrected, recorded on a Yanaco micro melting point apparatus. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254).

Materials

THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. MeOH was distilled with a small amount of magnesium and I_2. DMF was distilled under reduced pressure. Dichloromethane, benzene, MeCN were distilled from CaH_2, and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd.

第2章

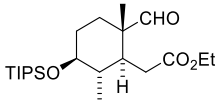
ethyl 2-((1*S*,2*S*,5*S*,6*S*)-2-((benzylthio)carbonyl)-2,6-dimethyl-5-((triisopropylsilyl)oxy)cyclohexyl)acetate (1a)



To a stirred solution of **1** (11.4 g, 23.3 mmol) in DMF (150 mL) were added K_2CO_3 (1.61 g, 11.6 mmol, 0.5 equiv) and BnSH (3.00 mL, 25.6 mmol, 1.1 equiv) at room temperature, and the reaction mixture was stirred for 4 h at 60 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (150 mL). The aqueous layer was extracted with Et_2O (100 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **1a** (9.20 g, 76%) as a colorless oil:

R_f = 0.52 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.18 (5H, m), 4.17-4.05 (4H, m), 3.42 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.46 (1H, ddd, *J* = 10.8, 7.9, 2.8 Hz), 2.19-2.07 (2H, m), 1.91-1.78 (2H, m), 1.66-1.39 (3H, m), 1.24 (3H, s), 1.24 (3H, dd, *J* = 7.4, 7.4 Hz), 1.06 (21H, s), 0.98 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.0, 172.8, 137.6, 128.8, 128.5, 127.1, 75.9, 60.4, 54.1, 42.9, 42.3, 36.3, 35.4, 33.1, 30.8, 18.2, 18.2, 15.5, 15.3, 14.1, 12.8; IR (neat) ν_{max} 2942, 2865, 1737, 1673, 1454, 1374, 1296, 1101, 985, 882, 793, 699, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{29}H_{48}NaO_4SSi$: 543.2935, found: 543.2937; $[\alpha]_D^{24}$ +5.2 (c = 0.16, $CHCl_3$).

ethyl 2-((1*S*,2*S*,5*S*,6*S*)-2-formyl-2,6-dimethyl-5-((triisopropylsilyl)oxy)cyclohexyl)acetate (2)



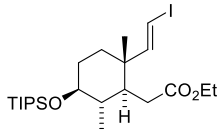
To a stirred solution of **1a** (7.09 g, 13.6 mmol) in acetone (100 mL) were added $Pd(OAc)_2$ (0.306 g, 1.36 mmol, 0.1 equiv) and Et_3SiH (3.46 mL, 40.8 mmol, 3.0 equiv) at room temperature, and the reaction mixture was stirred for 10 min. After disappearance of the starting material, to the reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford the product **2** (5.39 g, 90%) as a colorless oil:

R_f = 0.50 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (1H, s), 4.08 (2H, dddd, *J* = 3.4, 3.4, 3.4, 3.4 Hz), 3.40 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.23-2.12 (2H, m), 2.04-1.96 (1H, m), 1.95-1.88 (1H, m), 1.67-1.50 (2H, m), 1.48-1.39 (1H, m), 1.36 (1H, ddd, *J* = 12.5, 3.4, 3.4 Hz), 1.24 (3H, dd, *J* = 7.4, 7.4 Hz), 1.08-0.98 (27H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ 205.7, 173.1,

76.0, 60.6, 49.9, 41.4, 40.2, 35.8, 30.5, 29.9, 18.3, 18.2, 15.4, 14.1, 13.0, 12.8; IR (neat) ν_{max} 2942, 2866, 1728, 1461, 1375, 1300, 1106, 882, 803, 678 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{22}H_{42}NaO_4Si$: 421.2745, found: 421.2743; $[\alpha]_D^{24}$ +1.9 (c = 0.21, $CHCl_3$).

ethyl

2-((1*S*,2*S*,5*S*,6*S*)-2-((*E*)-2-iodovinyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetate (3)

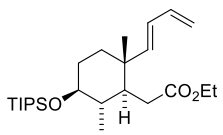


To a stirred solution of $CrCl_2$ (6.51 g, 52.9 mmol, 5.5 equiv) in dioxane (40 mL) were added CHI_3 (7.58 g, 19.2 mmol, 2.0 equiv) and **2** (4.24 g, 9.62 mmol) in THF (40 mL) at room temperature, and the reaction mixture was stirred for 8 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (80 mL). The aqueous layer was extracted with Et_2O (40 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **3** (3.41 g, 68%) as a yellow oil:

R_f = 0.73 (hexane/ethyl acetate = 8/1); ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (1H, d, *J* = 14.7 Hz), 6.06 (1H, d, *J* = 14.7 Hz), 4.19-4.07 (2H, m), 3.34 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.19 (1H, dd, *J* = 16.4, 3.4 Hz), 2.07 (1H, dd, *J* = 16.4, 7.9 Hz), 1.85-1.74 (2H, m), 1.62-1.36 (4H, m), 1.25 (3H, dd, *J* = 6.8, 6.8 Hz), 1.06 (21H, s), 0.96 (3H, s), 0.96 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 156.4, 77.5, 74.4, 60.8, 45.1, 44.9, 42.0, 37.3, 36.0, 31.4, 18.5, 18.5, 16.2, 15.9, 14.4, 13.1; IR (neat) ν_{max} 2940, 2865, 1734, 1461, 1373, 1241, 1108, 882, 802, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{23}H_{43}INaO_3Si$: 545.1918, found: 545.1919; $[\alpha]_D^{25}$ +5.0 (*c* 0.23, $CHCl_3$).

ethyl

2-((1*S*,2*R*,5*S*,6*S*)-2-((*E*)-buta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetate (5)

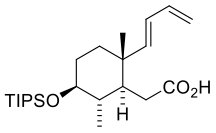


To a stirred solution of **3** (88.5 mg, 1.69 mmol) in DMF (16 mL) were added $PdCl_2(MeCN)_2$ (4.4 mg, 0.0169 mmol, 0.01 equiv) and tributylvinyltin **4** (59.1 mg, 1.86 mmol, 1.1 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added H_2O (15 mL). The aqueous layer was extracted with Et_2O (10 mL ×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **5** (0.716 g,

quant) as a colorless oil:

R_f = 0.73 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (1H, ddd, *J* = 17.0, 10.2, 10.2 Hz), 6.03 (1H, dd, *J* = 15.3, 10,2 Hz), 5.55 (1H, d, *J* = 15.3 Hz), 5.11 (1H, dd, *J* = 17.0, 1.7 Hz), 4.97 (1H, dd, *J* = 10.2, 1.7 Hz), 4.14-4.01 (2H, m), 3.36 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.23 (1H, dd, *J* = 16.4, 2.8 Hz), 2.04 (1H, dd, *J* = 16.4, 7.9 Hz), 1.81 (1H, ddd, *J* = 11.9, 7.9, 3.4 Hz), 1.75 (1H, ddd, *J* = 10.7, 7.9, 2.8 Hz), 1.61-1.50 (2H, m), 1.47-1.36 (2H, m), 1.22 (3H, dd, *J* = 6.8 Hz), 1.06 (21H, s), 0.98 (3H, s), 0.96 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 145.6, 137.6, 128.4, 115.3, 60.3, 45.6, 42.0, 39.9, 37.6, 35.9, 31.4, 29.7, 18.3, 18.2, 16.4, 15.7, 14.1, 12.9; IR (neat) ν_{max} 2940, 2866, 1736, 1648, 1602, 1463, 1373, 1103, 883, 803, 679 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{25}H_{46}NaO_3Si$: 445.3108, found: 445.109; $[\alpha]_D^{22}$ –18 (*c* 0.23, $CHCl_3$).

2-((1*S*,2*R*,5*S*,6*S*)-2-((*E*)-buta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetic acid (6)



To a stirred solution of $LiAlH_4$ (147 mg, 3.11 mmol, 2.0 equiv) in THF (10 mL) was added **5** (657 mg, 1.55 mmol) in THF (5 mL) at 0 ˚C, and the reaction mixture was stirred at 0 ˚C for 4 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 (3 mL), filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.17 (hexane/ethyl acetate = 8/1)

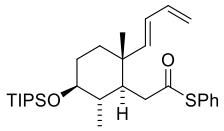
To a stirred solution of MS 4A (819 mg, 100 wt % against NMO) and NMO (819 g, 6.99 mmol, 4.5 equiv) in CH_2Cl_2 were added the above crude alcohol in CH_2Cl_2 (15 mL) and TPAP (27.3 g, 0.0777 mmol, 0.05 equiv.) at 0 ˚C, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.70 (hexane/ethyl acetate = 8/1)

To a stirred solution of the above crude aldehyde and 2-methyl-2-butene (0.0993 mL, 9.37 mmol, 10 equiv.) in *t*BuOH/H_2O (1/1, 15 mL) were added NaH_2PO_4 (225 mg, 1.87 mmol, 2.0 equiv) and $NaClO_2$ (127 mg, 1.41 mmol, 1.5 equi.) at room temperature, and the reaction mixture was stirred for 4 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **6** (357 mg, 64%) as a colorless oil:

R_f = 0.38 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (1H, ddd, *J* = 17.0, 10.2, 10.2 Hz), 6.04 (1H, dd, *J* = 15.3, 10,2 Hz), 5.54 (1H, d, *J* = 15.3 Hz), 5.12 (1H, dd, *J* = 17.0, 1.7 Hz),

4.98 (1H, dd, J = 10.2, 1.7 Hz), 3.36 (1H, ddd, J = 10.2, 10.2, 4.5 Hz), 2.30 (1H, dd, J = 17.0, 2.8 Hz), 2.09 (1H, dd, J = 17.0, 7.9 Hz), 1.81 (1H, ddd, J = 13.0, 7.9, 3.9 Hz), 1.72 (1H, ddd, J = 10.7, 7.9, 2.8 Hz), 1.61-1.37 (4H, m), 1.07 (21H, s), 1.01 (3H, d, J = 7.4 Hz), 0.99 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 145.3, 137.4, 128.7, 115.6, 76.7, 45.5, 42.0, 39.9, 37.6, 35.6, 31.4, 18.3, 18.3, 16.4, 15.8, 12.9; IR (neat) ν_{max} 2941, 2866, 1705, 1463, 1412, 1383, 1300, 1104, 1004, 882, 803, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{23}H_{42}NaO_3Si$: 417.2795, found: 417.2791; $[\alpha]_D^{29}$ –9.2 (*c* 0.70, $CHCl_3$).

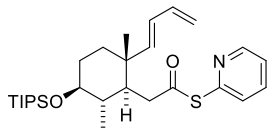
_S_-phenyl
2-((1*S*,2*R*,5*S*,6*S*)-2-((*E*)-buta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)ethan ethioate (7c)



To a stirred solution of **6** (259 mg, 0.656 mmol) in CH_2Cl_2 (6.5 mL) were added PhSH (0.067 mL, 0.656 mmol, 1.0 equiv) and DCC (203 mg, 0.984 mmol, 1.5 equiv), DMAP (8.0 mg, 0.0656 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 30 min. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (6.5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **7c** (278 mg, 87%) as a colorless oil:
R_f = 0.66 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (5H, s), 6.30 (1H, ddd, J = 16.4, 10.2, 10.2 Hz), 6.06 (1H, dd, J = 15.8, 10,2 Hz), 5.53 (1H, d, J = 15.8 Hz), 5.14 (1H, dd, J = 16.4, 1.7 Hz), 5.00 (1H, dd, J = 10.2, 1.7 Hz), 3.34 (1H, ddd, J = 10.2, 10.2, 4.5 Hz), 2.57 (1H, dd, J = 17.0, 2.8 Hz), 2.49 (1H, dd, J = 17.0, 7.9 Hz), 1.89 (1H, ddd, J = 10.7, 7.9, 2.8 Hz), 1.81 (1H, ddd, J = 12.5, 7.9, 3.4 Hz), 1.61-1.37 (4H, m), 1.07 (21H, s), 1.04 (3H, d, J = 6.8 Hz), 1.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 145.4, 137.5, 134.5, 129.2, 129.0, 128.7, 128.0, 115.6, 76.7, 45.7, 45.6, 42.1, 40.0, 37.6, 31.4, 18.3, 18.2, 16.5, 16.5, 12.9; IR (neat) ν_{max} 2940, 2865, 1716, 1461, 1441, 1382, 1243, 1105, 1007, 883, 744, 687 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{29}H_{46}NaO_2SSi$: 509.2880, found: 509.2884; $[\alpha]_D^{23}$ –53 (*c* 0.15, $CHCl_3$).

***S*-pyridin-2-yl**

2-((1*S*,2*R*,5*S*,6*S*)-2-((*E*)-buta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)ethan ethioate (7d)

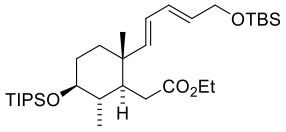


To a stirred solution of **6** (357 mg, 0.904 mmol) in CH_2Cl_2 (9 mL) were added 2-PySH (121 mg, 1.08 mmol, 1.2 equiv) and EDCI (260 mg, 1.36 mmol, 1.5 equiv), DMAP (11.0 mg, 0.0904 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (9 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **7d** (432 mg, 98%) as a colorless oil:

R_f = 0.37 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, dd, *J* = 5.1, 2.3 Hz), 7.71 (1H, ddd, *J* = 7.3, 7.3, 2.3 Hz), 7.58 (1H, d, *J* = 7.3 Hz), 7.26 (1H, ddd, *J* = 7.3, 5.1, 1.1 Hz), 6.29 (1H, ddd, *J* = 17.0, 10.2, 10.2 Hz), 6.05 (1H, dd, *J* = 15.8, 10,2 Hz), 5.53 (1H, d, *J* = 15.8 Hz), 5.13 (1H, dd, *J* = 17.0, 1.7 Hz), 4.99 (1H, dd, *J* = 10.2, 1.7 Hz), 3.35 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.64 (1H, dd, *J* = 16.4, 2.8 Hz), 2.52 (1H, dd, *J* = 16.4, 7.9 Hz), 1.90 (1H, ddd, *J* = 10.7, 8.5, 2.8 Hz), 1.81 (1H, ddd, *J* = 12.5, 8.5, 3.4 Hz), 1.61-1.36 (4H, m), 1.06 (21H, s), 1.04 (3H, d, *J* = 6.8 Hz), 1.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 151.8, 150.3, 145.1, 137.4, 136.9, 130.1, 128.8, 123.3, 115.8, 76.7, 46.3, 45.6, 42.1, 40.0, 37.5, 31.4, 18.3, 18.2, 16.6, 16.5, 12.9; IR (neat) ν_{max} 2940, 2864, 1708, 1648, 1602, 1572, 1450, 1420, 1150, 882, 801, 763, 712, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{45}NNaO_2SSi$: 510.2832, found: 510.2836; $[\alpha]_D^{26}$ –73 (*c* 0.33, $CHCl_3$).

ethyl

2-((1*S*,2*R*,5*S*,6*S*)-2-((1*E*,3*E*)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(tri isopropylsilyloxy)cyclohexyl)acetate (9)

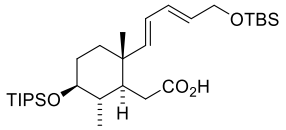


To a stirred solution of **3** (991 mg, 1.89 mmol) in DMF (18 mL) were added $PdCl_2(MeCN)_2$ (4.9 mg, 0.0189 mmol, 0.01 equiv) and stannane **8** (961 mg, 2.08 mmol, 1.1 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added H_2O (18 mL). The aqueous layer was extracted with Et_2O (10 mL × 2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash

chromatography (hexane/ethyl acetate = 50/1) to afford the product **9** (1.07 g, quant.) as a colorless oil:

R_f = 0.49 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1H, dd, *J* = 15.3, 10.2 Hz), 6.02 (1H, dd, *J* = 15.3, 10.2 Hz), 5.67 (1H, ddd, *J* = 15.3, 5.1, 5.1 Hz), 5.51 (1H, d, *J* = 15.3 Hz), 4.18 (2H, dd, *J* = 5.1, 1.1 Hz), 4.13-4.02 (2H, m), 3.36 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.23 (1H, dd, *J* = 16.4, 2.3 Hz), 2.02 (1H, dd, *J* = 16.4, 8.5 Hz), 1.80 (1H, ddd, *J* = 12.5, 7.9, 5.7 Hz), 1.74 (1H, ddd, *J* = 10.7, 7.9, 2.3 Hz), 1.60-1.49 (2H, m), 1.46-1.33 (3H, m), 1.25 (6H, s), 1.22 (2H, dd, *J* = 7.3, 7.3 Hz), 1.06 (21H, s), 0.97 (3H, s), 0.95 (3H, d, *J* = 6.8 Hz), 0.91 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 144.8, 130.8, 130.5, 127.2, 63.6, 60.3, 45.6, 42.0, 39.9, 37.7, 35.9, 31.5, 29.7, 26.0, 18.4, 18.3, 18.3, 16.5, 15.7, 14.1, 12.9; IR (neat) ν_{max} 2927, 2865, 1736, 1460, 1375, 1250, 1104, 837, 776, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{32}H_{62}NaO_4Si_2$: 589.4079, found: 589.4079; $[\alpha]_D^{23}$ –8.7 (*c* 0.36, $CHCl_3$).

2-((1*S*,2*R*,5*S*,6*S*)-2-((1*E*,3*E*)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetic acid (10)



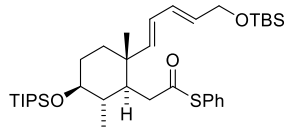
To a stirred solution of $LiAlH_4$ (368 mg, 3.46 mmol, 2.0 equiv) in THF (10 mL) was added **9** (981 mg, 1.73 mmol) in THF (5 mL) at 0 ˚C, and the reaction mixture was stirred at 0 ˚C for 8 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 (3.0 mL), filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.18 (hexane/ethyl acetate = 8/1)

To a stirred solution of MS 4A (811 mg, , 100 wt % against NMO) and NMO (811 mg, 6.92 mmol, 4.0 equiv) in CH_2Cl_2 were added the above crude alcohol in CH_2Cl_2 (15 mL) and TPAP (30.4 mg, 0.0865 mmol, 0.05 equiv) at 0 ˚C, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.72 (hexane/ethyl acetate = 8/1)

To a stirred solution of the above crude aldehyde and 2-methyl-2-butene (0.946 mL, 8.93 mmol, 10 equiv) in *t*BuOH/H_2O (1/1, 15 mL) were added NaH_2PO_4 (214 mg, 1.79 mmol, 2.0 equiv) and $NaClO_2$ (121 mg, 1.34 mmol, 1.5 equiv) at room temperature, and the reaction mixture was stirred for 4 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **10** (337 mg, 55%) as a colorless oil:

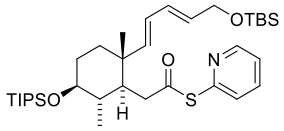
R_f = 0.42 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1H, dd, *J* = 15.3, 10.2 Hz), 6.03 (1H, dd, *J* = 15.3, 10.2 Hz), 5.68 (1H, ddd, *J* = 15.3, 5.1, 5.1 Hz), 5.50 (1H, d, *J* = 15.3 Hz), 4.18 (2H, dd, *J* = 5.1, 1.1 Hz), 3.36 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.32 (1H, dd, *J* = 17.0, 1.7 Hz), 2.05 (1H, dd, *J* = 17.0, 8.5 Hz), 1.81 (1H, ddd, *J* = 12.5, 7.9, 3.4 Hz), 1.70 (1H, ddd, *J* = 11.3, 7.9, 2.3 Hz), 1.61-1.50 (1H, m), 1.49-1.34 (3H, m), 1.06 (27H, s), 1.00 (3H, d, *J* = 6.2 Hz), 0.97 (3H, s), 0.91 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 144.4, 131.0, 130.4, 127.5, 65.9, 63.6, 45.5, 42.1, 39.9, 37.7, 35.7, 31.4, 26.0, 18.4, 18.3, 18.3, 16.5, 15.7, 15.2, 12.9; IR (neat) ν_{max} 2941, 2865, 1706, 1463, 1382, 1255, 1105, 837, 776, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{30}H_{58}NaO_4Si_2$: 561.3766, found: 561.3767; $[\alpha]_D^{24}$ –12 (*c* 0.38, $CHCl_3$).

_S_-phenyl
2-((1_S_,2_R_,5_S_,6_S_)-2-((1_E_,3_E_)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)ethanethioate (11a)



To a stirred solution of **10** (427 mg, 0.792 mmol) in CH_2Cl_2 (8 mL) were added PhSH (0.0854 mL, 0.832 mmol, 1.05 equiv) and DCC (245 mg, 1.19 mmol, 1.5 equiv), DMAP (9.7 mg, 0.0792 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 2 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **11a** (0.280 g, 56%) as a yellow oil:
R_f = 0.75 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (5H, s), 6.18 (1H, dd, *J* = 15.3, 10.2 Hz), 6.04 (1H, dd, *J* = 15.3, 10.2 Hz), 5.70 (1H, ddd, *J* = 15.3, 5.7, 5.7 Hz), 5.49 (1H, d, *J* = 15.3 Hz), 4.19 (2H, dd, *J* = 5.1, 1.1 Hz), 3.34 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.58 (1H, dd, *J* = 17.0, 2.3 Hz), 2.48 (1H, dd, *J* = 17.0, 7.9 Hz), 1.88 (1H, ddd, *J* = 10.7, 7.9, 2.3 Hz), 1.80 (1H, ddd, *J* = 13.0, 7.9, 4.5 Hz), 1.62-1.34 (4H, m), 1.07 (27H, s), 1.03 (3H, d, *J* = 6.8 Hz), 1.00 (3H, s), 0.91 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 144.5, 134.5, 131.1, 130.5, 129.2, 129.1, 128.1, 127.5, 63.6, 45.7, 45.6, 45.4, 42.2, 40.0, 37.7, 31.4, 26.0, 18.4, 18.3, 18.2, 16.6, 16.5, 12.9; IR (neat) ν_{max} 2927, 2864, 1712, 1461, 1440, 1382, 1251, 1102, 835, 743, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{36}H_{62}NaO_3SSi_2$: 653.3850, found: 653.3848; $[\alpha]_D^{28}$ –52 (*c* 0.32, $CHCl_3$).

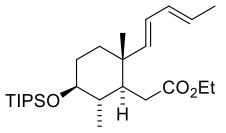
2-((1*S*,2*R*,5*S*,6*S*)-2-((1*E*,3*E*)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)ethanethioate (11b)



To a stirred solution of **10** (166 mg, 0.308 mmol) in CH_2Cl_2 (3.0 mL) were added 2-PySH (36.0 mg, 0.323 mmol, 1.05 equiv) and EDCI (88.9 mg, 0.462 mmol, 1.5 equiv), DMAP (3.8 mg, 0.0308 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 2 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 25/1) to afford the product **11b** (165 mg, 85%) as a colorless oil:

R_f = 0.42 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, dd, *J* = 4.5, 1.1 Hz), 7.71 (1H, ddd, *J* = 7.9, 7.9, 1.1 Hz), 7.58 (1H, ddd, *J* = 7.9, 1.1, 1.1 Hz), 7.28-7.24 (1H, m), 6.17 (1H, dd, *J* = 15.3, 10.7 Hz), 6.04 (1H, dd, *J* = 15.3, 10.7 Hz), 5.69 (1H, ddd, *J* = 15.3, 5.1, 5.1 Hz), 5.49 (1H, d, *J* = 15.3 Hz), 4.18 (2H, dd, *J* = 5.1, 1.1 Hz), 3.34 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.65 (1H, dd, *J* = 17.0, 2.3 Hz), 2.51 (1H, dd, *J* = 17.0, 7.9 Hz), 1.88 (1H, ddd, *J* = 10.7, 7.9, 2.3 Hz), 1.80 (1H, ddd, *J* = 13.0, 7.9, 4.0 Hz), 1.64-1.34 (4H, m), 1.06 (27H, s), 1.04 (3H, d, *J* = 6.8 Hz), 1.00 (3H, s), 0.90 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 151.9, 150.3, 144.2, 136.9, 131.3, 130.3, 130.1, 127.6, 123.3, 63.6, 46.3, 45.7, 42.1, 40.3, 40.0, 37.7, 31.4, 26.0, 18.4, 18.3, 18.2, 16.7, 16.6, 12.9; IR (neat) ν_{max} 2928, 2864, 1709,1573, 1461, 1451, 1252, 1102, 835, 763, 736, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{61}NNaO_3SSi_2$: 654.3803, found: 654.3801; $[\alpha]_D^{28}$ –53 (*c* 0.32, $CHCl_3$).

ethyl
2-((1*S*,2*R*,5*S*,6*S*)-2,6-dimethyl-2-((1*E*,3*E*)-penta-1,3-dien-1-yl)-5-((triisopropylsilyl)oxy)cyclohexyl)acetate (13)

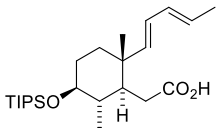


To a stirred solution of phenyltetrazole **12** (195 mg, 0.738 mmol, 3.0 equiv) in DME (3mL) was added KHMDS (0.5M in toluene, 1.48 mL, 0.738 mmol, 3.0 equiv) at –60 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution, **2** (98.1 mg, 246 mmol) in DME (1 mL×3) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous

NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford the product **13** (73.1 mg, 68%) as colorless oil:

R_f = 0.74 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06-6.00 (2H, m), 5.60 (1H, dq, *J* = 6.8, 6.8 Hz), 5.40 (1H, d, *J* = 13.0 Hz), 4.14-4.00 (2H, m), 3.35 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.24 (1H, dd, *J* = 15.9, 2.8 Hz), 2.02 (1H, dd, *J* = 15.9, 7.9 Hz), 1.84-1.69 (5H, m), 1.62-1.50 (1H, m), 1.47-1.33 (3H, m), 1.22 (3H, dd, *J* = 6.8, 6.8 Hz), 1.06 (24H, s), 0.96 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 174.4, 142.4, 132.0, 127.8, 127.4, 60.2, 45.7, 42.0, 39.7, 37.8, 35.9, 31.5, 18.3, 18.2, 18.0, 16.5, 15.7, 14.1, 12.9; IR (neat) ν_{max} 2941, 2866, 1736, 1463, 1373, 1103, 990, 883, 805, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{48}NaO_3Si$: 459.3265, found: 459.3266; $[\alpha]_D^{24}$ = -14 (c = 0.47, $CHCl_3$).

2-((1*S*,2*R*,5*S*,6*S*)-2,6-dimethyl-2-((1*E*,3*E*)-penta-1,3-dien-1-yl)-5-((triisopropylsilyl)oxy)cyclohexyl)acetic acid (14)



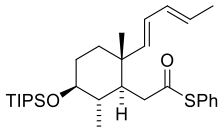
To a stirred solution of $LiAlH_4$ (18.8 mg, 0.397 mmol, 2.0 equiv) in THF (1 mL) was added **13** (86.6 mg, 0.198 mmol) in THF (1 mL×3) at 0 ˚C, and the reaction mixture was stirred at 0 ˚C for 8 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 (3 mL), filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.34 (hexane/ethyl acetate = 4/1)

To a stirred solution of MS 4A (104 mg, 100 wt % against NMO) and NMO (104 mg, 0.892 mmol, 4.5 equiv) in CH_2Cl_2 (1 mL) were added the above crude alcohol in CH_2Cl_2 (1 mL×3) and TPAP (3.5 mg, 0.0099.mmol, 0.05 equiv.) at 0 ˚C, and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was used for the next step without further purification. R_f =0.75 (hexane/ethyl acetate = 4/1)

To a stirred solution of the above crude aldehyde and 2-methyl-2-butene (0.21 mL, 1.983 mmol, 10 equiv.) in *t*BuOH/H_2O (1/1, 5 mL) were added NaH_2PO_4 (47.6 mg, 0.0.397 mmol, 2.0 equiv) and $NaClO_2$ (26.9 mg, 0.298 mmol, 1.5 equi.) at room temperature, and the reaction mixture was stirred for 24 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **14** (47.8 mg, 59%) as a colorless oil:

R_f = 0.45 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08-5.92 (1H, m), 5.71-5.20 (3H, m), 3.40-3.31 (1H, m), 2.34 (1H, dddd, *J* = 16.4, 11.9, 4.5, 2.3 Hz), 2.06 (1H, dd, *J* = 16.4, 7.4 Hz), 1.85-1.14 (6H, m), 1.06 (21H, s), 1.00 (3H, d, *J* = 6.3 Hz), 0.97 (3H, s), 0.93 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 180.4142.1, 131.8, 128.1, 127.8, 45.6, 42.0, 39.5, 37.8, 35.4, 31.5, 18.3, 18.2, 18.0, 16.5, 15.9, 12.9; IR (neat) ν_{max} 2941, 2866, 1704, 1460, 1102, 882, 803, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{24}H_{44}NaO_3Si$: 431.2952, found: 431.2953; $[\alpha]_D^{26}$ = -3.8 (c = 0.35, $CHCl_3$).

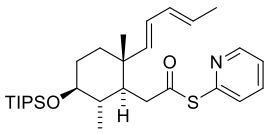
_S_-phenyl
2-((1_S_,2_R_,5_S_,6_S_)-2,6-dimethyl-2-((1_E_,3_E_)-penta-1,3-dien-1-yl)-5-((triisopropylsilyl)oxy)cyclohexyl)ethanethioate (15a)



To a stirred solution of **14** (118 mg, 0.303 mmol) in EtOAc (5 mL) were added PhSH (0.031 mL, 0.303 mmol, 1.00 equiv) and DCC (62.5 mg, 0.303 mmol, 1.0 equiv), DMAP (3.7 mg, 0.0303 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 15 min. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 80 / 1) to afford the product **15a** (63.7 mg, 42%) as a yellow oil:

R_f = 0.79 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (5H, s), 6.07-5.94 (2H, m), 5.64 (1H, ddd, *J* = 14.2, 14.2, 6.8 Hz), 5.46-5.33 (1H, m), 3.34 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.69-2.55 (1H, m), 2.48 (1H, dd, *J* = 16.4, 7.9 Hz), 1.96-1.70 (5H, m), 1.66 (1H, dd, *J* = 6.2, 1.7 Hz), 1.63-1.16 (3H, m), 1.07 (21H, s), 1.04 (3H, d, *J* = 6.8 Hz), 0.99 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.5, 142.2, 134.5, 132.0, 129.2, 129.0, 128.1, 128.0, 127.7, 45.8, 45.7, 42.1, 39.9, 37.8, 34.9, 31.5, 18.3, 18.3, 18.0, 16.6, 12.9; IR (neat) ν_{max} 2939, 2865, 2119, 1713, 1460, 1440, 1382, 1103, 988, 882, 744, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{30}H_{48}NaO_2SSi$: 523.3036, found: 523.3041; $[\alpha]_D^{27}$ = -54 (c = 0.18, $CHCl_3$).

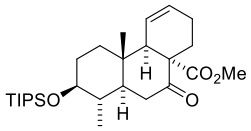
_S_-(pyridin-2-yl)
2-((1_S_,2_R_,5_S_,6_S_)-2,6-dimethyl-2-((1_E_,3_E_)-penta-1,3-dien-1-yl)-5-((triisopropylsilyl)oxy)cyclohexyl)ethanethioate (15b)



To a stirred solution of **14** (23.6 mg, 0.0578 mmol) in CH_2Cl_2 (3.0 mL) were added 2-PySH (6.8 mg, 0.0606 mmol, 1.05 equiv) and EDCI (16.6 mg, 0.0867 mmol, 1.5 equiv), DMAP (0.7 mg, 0.0058 mmol, 0.1 equiv) at room temperature, and the reaction mixture was stirred for 4 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL×2), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **15b** (3.7 mg, 13%) as a colorless oil:

R_f = 0.51 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, dd, *J* = 4.5, 1.1 Hz), 7.71 (1H, ddd, *J* = 7.9, 7.9, 1.7 Hz), 7.58 (1H, d, *J* = 7.9 Hz), 7.28-7.24 (1H, m), 6.00 (1H, d, *J* = 14.7 Hz), 6.00 (1H, dd, *J* = 19.3, 10.2 Hz), 5.66-5.57 (1H, m), 5.44-5.33 (1H, m), 3.34 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.66 (1H, dd, *J* = 16.4, 2.3 Hz), 2.51 (1H, dd, *J* = 16.4, 7.9 Hz), 1.94-1.70 (5H, m), 1.61-1.16 (4H, m), 1.06 (21H, s), 1.04 (3H, d, *J* = 6.2 Hz), 0.99 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 196.5, 151.9, 150.3, 142.0, 136.9, 131.9, 130.1, 128.2, 127.9, 123.3, 46.3, 45.9, 42.1, 39.9, 37.8, 31.5, 29.7, 18.3, 18.2, 18.0, 16.7, 16.6, 12.9; IR (neat) ν_{max} 2940, 2865, 1710, 1573, 1561, 1450, 1420, 1104, 988, 882, 764, 678 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{29}H_{47}NNaO_2SSi$: 524.2989, found: 524.2992; $[\alpha]_D^{24.6}$ = -69 (c = 0.13, $CHCl_3$).

(1*S*,2*S*,4a*S*,4b*R*,8a*S*,10a*S*)-methyl 1,4a-dimethyl-9-oxo-2-(triisopropylsilyloxy)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydrophenanthrene-8a-carboxylate (17)

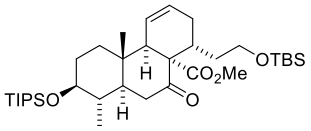


To a stirred solution of **7d** (31.2 mg, 0.0640 mmol) and stannane **16a** (48.0 mg, 0.128 mmol, 2.0 equiv) in THF (1.3 mL) were added $Pd_2(dba)_3$ (5.9 mg, 0.00640 mmol, 0.1 equiv), $AsPh_3$ (5.9 mg, 0.0192 mmol, 0.3 equiv) and CuTC (36.6 mg, 0.192 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1×2) to afford the product **17** (11.7 mg, 81%) as a colorless oil:

R_f = 0.44 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, m), 5.65 (1H, m), 3.70 (3H, s), 3.35 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.88 (1H, br), 2.61 (1H, dd, *J* = 17.0, 4.5 Hz), 2.27 (1H, m), 2.19 (1H, dd, *J* = 17.0, 13.0 Hz), 2.12 (1H, m), 2.06 (1H, m), 1.91-1.83 (3H, m), 1.62-1.47 (2H, m), 1.42-1.27 (2H, m), 1.07 (21H, s), 0.98 (3H, d, *J* = 6.2 Hz), 0.87 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 172.8, 128.7, 124.2, 77.3, 58.9, 52.6, 49.7, 46.5, 40.8, 39.5, 37.2, 36.8, 31.0, 26.2, 22.0, 18.3, 18.2, 15.3, 14.7, 12.9; IR (neat) ν_{max} 2925, 2865, 1736, 1707, 1460,

1234, 1103, 1060, 883, 809, 678 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{27}H_{46}NaO_4Si$: 485.3058, found: 485.3057; $[\alpha]_D^{28}$ +3.1 (*c* 0.07, $CHCl_3$).

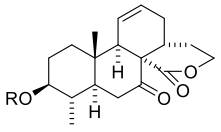
(1*S*,2*S*,4a*S*,4b*R*,8*R*,8a*S*,10a*S*)-methyl 8-(2-(tert-butyldimethylsilyloxy)ethyl)-1,4a-dimethyl-9-oxo-2-(triisopropylsilyloxy)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydrophenanthrene-8a-carboxylate (18)



To a stirred solution of **7c** (25.6 mg, 0.0525 mmol) and stannane **16b** (56.0 mg, 0.105 mmol, 2.0 equiv) in THF (1.1 mL) were added $Pd_2(dba)_3$ (4.8 mg, 0.00525 mmol, 0.1 equiv), $AsPh_3$ (4.8 mg, 0.0158 mmol, 0.3 equiv) and CuTC (30.0 mg, 0.1575 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **18** (21.0 mg, 66%) as a colorless oil:

R_f = 0.58 (hexane/ethyl acetate = 8/1); ^1H NMR (500 MHz, $CDCl_3$) δ 5.85-5.77 (1H, m), 5.68-5.60 (1H, m), 3.67 (3H, s), 3.63-3.49 (2H, m), 3.38-3.28 (1H, m), 2.94 (1H, d, *J* = 4.5 Hz), 2.65-2.57 (1H, m), 2.47 (1H, dd, *J* = 14.7, 2.8 Hz), 2.35-2.22 (2H, m), 2.15-2.03 (1H, m), 1.85 (2H, d, *J* = 10.7 Hz), 1.72 (1H, dd, *J* = 14.1, 9.6 Hz), 1.51-1.38 (3H, d, *J* = 6.2 Hz), 1.36-1.23 (2H, d, *J* = 6.2 Hz), 1.07 (27H, s), 0.97 (3H, s), 0.87 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 172.2, 128.5, 124.8, 76.8, 64.4, 60.6, 52.1, 52.0, 40.2, 39.6, 37.6, 37.2, 34.0, 31.0, 30.3, 28.0, 26.0, 26.0, 25.9, 18.3, 18.2, 18.2, 15.4, 15.4, 12.9; IR (neat) ν_{max} 2945, 2865, 1736, 1702, 1462, 1387, 1096, 834, 736, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{64}NaO_5Si_2$: 643.4184, found: 643.4181; $[\alpha]_D^{24}$ –0.63 (*c* 0.96, $CHCl_3$).

(3a*R*,7a*S*,9a*S*,10*S*,11*S*,13a*S*,13b*R*)-3,3a,4,5,7,8,9,9a,10,11,12,13,13a,13b-tetradecahydro-10,13a-dimethyl-7,8-dioxonaphtho[1,2-i]isochromen-11-yl 3,5-dinitrobenzoate (18')



R = diNO2Bz

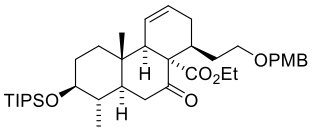
To a stirred solution of **18** (13.8 mg, 0.0222 mmol) in THF was added TBAF (1.0 M in THF, 0.067 mL, 0.0666 mmol, 3.0 equiv), and the reaction mixture was stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next step without further

purification.

To a stirred solution of the residue in CH_2Cl_2 (1.0 mL) were added DMAP (cat.) and 3,5-diNO_2BzCl (excess), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 50/1 × 3) to afford **18'** (3.2 mg, 28% over 2 steps):

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (1H, dd, *J* = 2.1, 2.1 Hz), 9.16 (2H, d, *J* = 2.1 Hz), 5.91 (1H, ddd, *J* = 10.3, 3.4, 3.4 Hz), 5.84-5.79 (1H, m), 4.81 (1H, ddd, *J* = 11.0, 11.0, 5.1 Hz), 4.53-4.42 (2H, m), 3.19 (1H, d, *J* = 4.9 Hz), 2.84-2.76 (1H, m), 2.69 (1H, dd, *J* = 14.8, 3.7 Hz), 2.45 (1H, dd, *J* = 14.0, 14.0 Hz), 2.34 (1H, ddddd, *J* = 18.7, 3.5, 3.5, 35, 3.5 Hz), 2.20-2.08 (2H, m), 2.06-1.89 (3H, m), 1.82-1.69 (3H, m), 1.52 (1H, dd, *J* = 14.4, 4.3 Hz), 1.11 (3H, s), 0.96 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.6, 170.5, 162.0, 148.7, 134.1, 129.4, 127.5, 125.6, 122.4, 80.6, 65.5, 61.4, 49.8, 48.2, 39.1, 37.6, 36.6, 36.5, 28.9, 27.8, 26.3, 24.4, 15.1, 14.8; IR (neat) ν_{max} 3103, 2926, 1724, 1697, 1623, 1542, 1459, 1344, 1272, 1164, 721 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{28}N_2NaO_9$: 535.1687, found: 535.1690; $[\alpha]_D^{27}$ +36 (*c* 0.095, $CHCl_3$).

(1*S*,2*S*,4a*S*,4b*R*,8*S*,8a*S*,10a*S*)-ethyl 8-(2-(4-methoxybenzyloxy)ethyl)-1,4a-dimethyl-9-oxo-2-(triisopropylsilyloxy)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydrophenanthrene-8a-carboxylate (19)

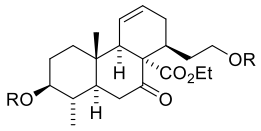


To a stirred solution of **7c** (27.0 mg, 0.0554 mmol) and stannane **16c** (61.3 mg, 0.111 mmol, 2.0 equiv) in THF (1.1 mL) were added $Pd_2(dba)_3$ (5.8 mg, 0.0055 mmol, 0.1 equiv), $AsPh_3$ (5.8 mg, 0.0166 mmol, 0.3 equiv) and CuTC (31.7 g, 0.166 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **19** (11.4 g, 32%) as a colorless oil:

R_f = 0.34 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 5.83-5.77 (1H, m), 5.49 (1H, ddd, *J* = 10.7, 2.8, 2.8 Hz), 4.39 (1H, d, *J* = 11.3 Hz), 4.34 (1H, d, *J* = 11.3 Hz), 4.30 (1H, m), 4.15 (1H, m), 3.80 (3H, s), 3.44-3.23 (4H, m), 2.87 (1H, dd, *J* = 17.0, 6.2 Hz), 2.27(1H, m), 2.06-1.95 (2H, m), 1.91-1.77 (4H, m), 1.49-1.23 (8H, m), 1.06 (21H, s), 0.96 (3H, d, *J* = 6.2 Hz), 0.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 174.3, 159.0, 130.7, 129.1, 126.7, 125.4, 113.7, 76.7, 76.6, 72.3, 68.6, 61.7, 60.5, 55.3, 53.9, 44.0, 43.0, 41.4, 39.2, 38.3, 36.7, 31.3, 30.3, 26.5, 18.3, 18.2, 15.8, 14.0, 12.9; IR (neat) ν_{max} 2921, 2851, 1736,

1709, 1513, 1462, 1096, 882, 808, 737, 677 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{38}H_{60}NaO_6Si$: 663.4051, found: 663.4050; $[\alpha]_D^{27}$ + 42 (*c* 0.12, $CHCl_3$).

(1*S*,2*S*,4a*S*,4b*R*,8*S*,8a*S*,10a*S*)-ethyl 2-(3,5-dinitrobenzoyloxy)-8-(2-(3,5-dinitrobenzoyloxy)ethyl)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethyl-9-oxophenanthrene-8a-carboxylate (19')



R = diNO_2Bz

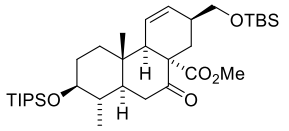
To a stirred solution of **19** (16.8 mg, 0.0267 mmol) in THF was added TBAF (1.0 M in THF, 0.080 mL, 0.0801 mmol, 3.0 equiv), and the reaction mixture was stirred for 4 h at 50 °C. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next step without further purification.

To a stirred solution of the residue in CH_2Cl_2/H_2O (1/1) was added DDQ (18.1 mg, 0.0801 mmol, 3.0 equiv), and the reaction mixture was stirred for 1 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by short column to afford a colorless oil.

To a stirred solution of the residue in CH_2Cl_2 were added DMAP ((4.9 mg, 0.0400 mmol, 1.5 equiv) and 3,5-diNO_2BzCl (6.5 mg, 0.0280 mmol, 1.05 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 50/1 × 3) to afford **19'** as a colorless oil (5.2 mg, 26% over 3 steps):

^1H NMR (600 MHz, $CDCl_3$) δ 9.16 (2H, ddd, *J* = 2.3, 2.3, 2.3 Hz), 9.08 (4H, dd, *J* = 2.3, 0.9 Hz), 5.87-5.82 (1H, m), 5.49 (1H, ddd, *J* = 10.5, 2.7, 2.7 Hz), 4.77 (1H, ddd, *J* = 10.3, 10.3, 4.2 Hz), 4.41-4.31 (2H, m), 4.26-4.19 (1H, m), 3.25 (1H, s), 2.91 (1H, dd, *J* = 18.3, 6.8 Hz), 2.36-2.28 (1H, m), 2.24-2.17 (1H, m), 2.08 (1H, ddd, *J* = 17.5, 6.0, 6.0 Hz), 2.00-1.91 (3H, m), 1.89-1.74 (3H, m), 1.65-1.44 (4H, m), 1.30 (3H, dd, *J* = 7.2, 7.2 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 0.70 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 174.5, 163.0, 162.5, 149.1, 134.5, 134.3, 129.8, 129.8, 129.7, 127.1, 125.7, 122.8, 122.8, 80.7, 65.8, 62.6, 60.9, 54.2, 44.3, 42.8, 38.9, 38.5, 38.0, 37.1, 30.1, 27.3, 26.9, 16.8, 15.7, 14.6; IR (neat) ν_{max} 3100, 2973, 1725, 1707, 1628, 1541, 1459, 1343, 1275, 1166, 1075, 920, 720 cm^{-1}; HRMS-ESI $[M+Cl]^-$ calculated for $C_{35}H_{36}ClN_4O_{15}$: 787.1871, found: 787.1887; $[\alpha]_D^{28}$ +39 (*c* 0.14, $CHCl_3$).

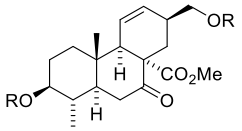
(1*S*,2*S*,4a*S*,4b*R*,7*S*,8a*S*,10a*S*)-methyl 7-((tert-butyldimethylsilyloxy)methyl)-1,4a-dimethyl-9-oxo-2-(triisopropylsilyloxy)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydrophenanthrene-8a-carboxylate (20)



To a stirred solution of **11b** (29.3 mg, 0.0463 mmol) and stannane **16a** (43.5 mg, 0.0926 mmol, 2.0 equiv) in THF (0.95 mL) were added $Pd_2(dba)_3$ (4.2 mg, 0.00463 mmol, 0.1 equiv), $AsPh_3$ (4.2 mg, 0.0139 mmol, 0.3 equiv) and CuTC (26.5 mg, 0.139 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **20** (17.4 mg, 62%) as a colorless oil:

R_f = 0.57 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (1H, d, *J* = 10.7 Hz), 5.70 (1H, ddd, *J* = 10.7, 4.5, 2.3 Hz), 3.70 (3H, s), 3.61 (1H, dd, *J* = 10.2, 5.7 Hz), 3.51 (1H, dd, *J* = 9.7, 5.7 Hz), 3.35 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.78 (1H, s), 2.61 (2H, dd, *J* = 17.5, 4.5 Hz), 2.27-2.16 (2H, m), 1.87 (2H, d, *J* = 12.5 Hz), 1.68-1.23 (5H, m), 1.08 (27H, s), 0.99 (3H, d, *J* = 6.8 Hz), 0.92 (3H, s), 0.88 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 172.6, 131.2, 124.8, 77.3, 66.7, 59.6, 52.6, 49.9, 47.1, 40.5, 39.1, 36.9, 36.6, 35.8, 31.0, 29.7, 29.1, 26.0, 25.9, 18.3, 18.2, 15.2, 14.8, 12.9; IR (neat) ν_{max} 2925, 2855, 1809, 1732, 1702, 1461, 1381, 1250, 1069, 835, 775, 675 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{34}H_{62}NaO_5Si_2$: 629.4028, found: 629.4028; $[\alpha]_D^{28}$ –24 (*c* 0.19, $CHCl_3$).

(1*S*,2*S*,4a*S*,4b*R*,7*S*,8a*S*,10a*S*)-methyl 2-(3,5-dinitrobenzoyloxy)-7-((3,5-dinitrobenzoyloxy)methyl)-1,2,3,4,4a,4b,7,8,8a,9,10,10a-dodecahydro-1,4a-dimethyl-9-oxophenanthrene-8a-carboxylate (20')



R = diNO_2Bz

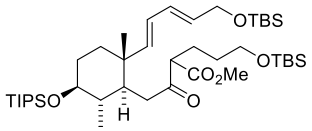
To a stirred solution of **20** (10.8 mg, 0.0178 mmol) in THF was added TBAF (1.0 M in THF, 0.053 mL, 0.0534 mmol, 3.0 equiv), and the reaction mixture was stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next step without further purification.

To a stirred solution of the residue in CH_2Cl_2 were added DMAP (cat.) and 3,5-diNO_2BzCl (excess),

and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 50/1 × 3) to afford **20'** (5.6 mg, 43% over 2 steps):

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (2H, dd, *J* = 2.3, 2.3 Hz), 9.17 (2H, d, *J* = 2.3 Hz), 9.14 (2H, d, *J* = 2.3 Hz), 5.89 (2H, s), 4.87 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 4.54 (1H, dd, *J* = 10.7, 5.7 Hz), 4.41 (1H, dd, *J* = 10.7, 5.1 Hz), 3.76 (3H, s), 3.16-3.07 (1H, m), 2.94 (1H, s), 2.78 (1H, dd, *J* = 17.0, 4.5 Hz), 2.47 (1H, dd, *J* = 13.6, 5.7 Hz), 2.31 (1H, dd, *J* = 17.5, 12.5 Hz), 2.14 (1H, ddd, *J* = 12.5, 8.5, 4.0 Hz), 2.06 (1H, ddd, *J* = 13.6, 3.4, 3.4 Hz), 1.92-1.74 (3H, m), 1.65 (1H, dd, *J* = 13.6, 10.7 Hz), 1.60 (1H, dd, *J* = 13.6, 3.4 Hz), 1.06 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 175.7, 171.8, 162.5, 162.1, 151.5, 148.7, 134.0, 133.7, 129.4, 129.4, 126.3, 122.6, 122.5, 77.2, 76.9, 69.6, 58.6, 49.5, 46.3, 39.1, 37.1, 36.8, 36.1, 32.7, 29.4, 26.4, 14.9, 14.5; IR (neat) ν_{max} 3101, 2951, 1726, 1701, 1628, 1541, 1459, 1343, 1272, 1164, 720 cm^{-1}; HRMS-ESI $[M+Cl]^-$ calculated for $C_{33}H_{32}Cl\,N_4O_{15}$: 759.1558, found: 759.1560; $[\alpha]_D^{28}$ –30 (*c* 0.18, $CHCl_3$).

(*Z*)-methyl 5-(tert-butyldimethylsilyloxy)-2-(2-((1*S*,2*R*,5*S*,6*S*)-2-((1*E*,3*E*)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetyl)pent-2-enoate (21)

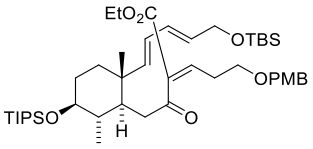


To a stirred solution of **11a** (33.6 mg, 0.0531 mmol) and stannane **16b** (56.6 mg, 0.106 mmol, 2.0 equiv) in THF (1.1 mL) were added $Pd_2(dba)_3$ (4.7 mg, 0.00531 mmol, 0.1 equiv), $AsPh_3$ (4.9 mg, 0.0159 mmol, 0.3 equiv) and CuTC (30.4 mg, 0.159 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **21** (24.3 mg, 58%) as a colorless oil:

R_f = 0.58 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 7.4 Hz), 6.14 (1H, dd, *J* = 14.7, 10.2 Hz), 5.99 (1H, dd, *J* = 14.7, 10.2 Hz), 5.65 (1H, ddd, *J* = 14.7, 5.1, 5.1 Hz), 5.47 (1H, d, *J* = 15.8 Hz), 4.17 (2H, d, *J* = 5.7 Hz), 3.83 (3H, s), 3.73 (2H, dd, *J* = 6.3, 6.3 Hz), 3.36 (1H, ddd, *J* = 10.2, 10.2, 4.5 Hz), 2.59-2.50 (2H, m), 2.33 (1H, d, *J* = 17.0 Hz), 2.00 (1H, dd, *J* = 9.6, 9.6 Hz), 1.86-1.21 (6H, m), 1.05 (33H, s), 0.98 (3H, s), 0.90 (9H, s), 0.88 (9H, s), 0.83 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 166.9, 144.8, 137.6, 130.8, 130.5, 129.5, 127.2, 63.6, 61.3, 59.7, 52.0, 43.5, 42.1, 40.7, 40.1, 39.9, 37.8, 33.4, 31.5, 29.7, 26.0, 25.8, 18.4, 18.3, 18.2, 16.8, 16.6, 12.9; IR (neat) ν_{max} 2928, 2861, 1732, 1462, 1381, 1361, 1098, 833, 775, 676 cm^{-1};

HRMS-ESI $[M+Na]^+$ calculated for $C_{42}H_{80}NaO_6Si_3$: 787.5155, found: 787.5148; $[\alpha]_D^{29}$ +2.4 (*c* 0.42, $CHCl_3$).

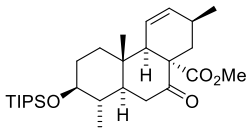
(*E*)-ethyl 5-(4-methoxybenzyloxy)-2-(2-((1*S*,2*R*,5*S*,6*S*)-2-((1*E*,3*E*)-5-(tert-butyldimethylsilyloxy)penta-1,3-dienyl)-2,6-dimethyl-5-(triisopropylsilyloxy)cyclohexyl)acetyl)pent-2-enoate (22)



To a stirred solution of **11a** (34.0 mg, 0.0538 mmol) and stannane **16c** (59.5 mg, 0.108 mmol, 2.0 equiv) in THF (1.1 mL) were added $Pd(PPh_3)_4$ (12.2 mg, 0.0108 mmol, 0.2 equiv), $AsPh_3$ (4.9 mg, 0.0161 mmol, 0.3 equiv) and CuTC (30.8 g, 0.0161 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **22** (15.2 mg, 36%) as a colorless oil:

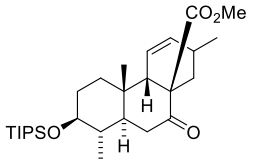
R_f = 0.35 (hexane/ethyl acetate = 8/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 9.0 Hz), 6.97 (1H, dd, *J* = 7.4, 7.4 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 6.11 (1H, dd, *J* = 14.7, 10.2 Hz), 5.96 (1H, dd, *J* = 14.7, 10.2 Hz), 5.61 (1H, ddd, *J* = 14.7, 5.1, 5.1 Hz), 5.46 (1H, d, *J* = 14.7 Hz), 4.41 (2H, s), 4.21 (2H, q, *J* = 6.8 Hz), 4.13 (2H, d, *J* = 4.5 Hz), 3.80 (3H, s), 3.50 (2H, ddd, *J* = 6.3, 6.3, 1.1 Hz), 3.39 (1H, ddd, *J* = 10.7, 10.7, 4.5 Hz), 2.57-2.51 (2H, m), 2.44-2.36 (2H, m), 2.05-1.97 (1H, m), 1.85-1.75 (1H, m), 1.41-1.30 (4H, m), 1.27 (3H, t, *J* = 6.8 Hz), 1.26 (6H, s), 1.07 (21H, s), 0.95 (3H, d, *J* = 6.8 Hz), 0.93 (3H, s), 0.89 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 164.5, 159.2, 145.5, 144.8, 136.8, 130.8, 130.4, 130.3, 129.3, 127.0, 113.8, 72.6, 68.1, 63.5, 61.1, 55.3, 41.9, 41.8, 39.9, 37.7, 31.5, 30.0, 29.7, 25.9, 18.3, 18.3, 18.3, 18.2, 16.8, 16.3, 14.2,12.9, 12.9; IR (neat) ν_{max} 2928, 2863, 1708, 1612, 1513, 1463, 1363, 1247, 1095, 836, 736, 676 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{45}H_{76}NaO_7Si_2$: 807.5022, found: 807.5015; $[\alpha]_D^{25}$ +2.7 (*c* 0.13, $CHCl_3$).

methyl (1*S*,2*S*,4a*S*,4b*R*,7*S*,8a*S*,10a*S*)-1,4a,7-trimethyl-9-oxo-2-((triisopropylsilyl)oxy)-1,3,4,4a,4b,7,8,9,10,10a-decahydrophenanthrene-8a(2*H*)-carboxylate (23)



methyl (1*S*,2*S*,4a*S*,4b*S*,8a*R*,10a*S*)-1,4a,7-trimethyl-9-oxo-2-((triisopropylsilyl)oxy)-1,3,4,4a,4b,7,8,9,10,

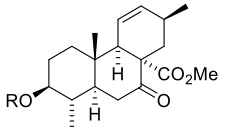
10a-decahydrophenanthrene-8a(2*H*)-carboxylate (24)



To a stirred solution of **15a** (32.2 mg, 0.0643 mmol) and stannane **16a** (48.2 mg, 0.129 mmol, 2.0 equiv) in THF (1 mL) were added $Pd_2(dba)_3$ (5.9 mg, 0.0064 mmol, 0.1 equiv), $AsPh_3$ (5.9 mg, 0.0193 mmol, 0.3 equiv) and CuTC (36.8 mg, 0.193 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 8/1 × 2) to afford the product **23** and **24** (14.6 mg, 47%) as a colorless oil:

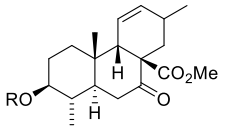
Ratio (5/ 1) R_f = 0.33 (hexane/ethyl acetate = 20/1, twice); HRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{48}NaO_4Si$: 499.3214, found: 499.3216.

methyl (1*S*,2*S*,4a*S*,4b*R*,7*S*,8a*S*,10a*S*)-1,4a,7-trimethyl-2-((4-nitrobenzoyl)oxy)-9-oxo-1,3,4,4a,4b,7,8,9,10,10a-decahydrophenanthrene-8a(2*H*)-carboxylate (23')



R = diNO$_2$Bz

methyl (1*S*,2*S*,4a*S*,4b*S*,8a*R*,10a*S*)-1,4a,7-trimethyl-2-((4-nitrobenzoyl)oxy)-9-oxo-1,3,4,4a,4b,7,8,9,10,10a-decahydrophenanthrene-8a(2*H*)-carboxylate (24')



R = diNO$_2$Bz

To a stirred solution of **23** and **24** (27.5 mg) in THF was added TBAF (3.0 equiv), and the reaction mixture was stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next step without further purification.

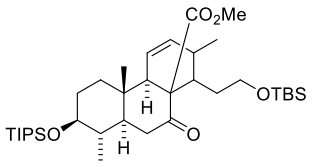
To a stirred solution of the residue in CH_2Cl_2 were added DMAP (cat.) and 3,5-diNO$_2$BzCl (excess), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution. The aqueous

layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 50/1×3) to afford **23'** (3.8 mg) and **24'** (1.0 mg):

23' (major): R_f = 0.61 (hexane/ethyl acetate = 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (1H, dd, *J* = 2.2, 2.2 Hz), 9.16 (2H, d, *J* = 2.0 Hz), 5.77 (1H, d, *J* = 10.3 Hz), 5.69 (1H, ddd, *J* = 10.3, 3.8, 2.3 Hz), 4.78 (1H, ddd, *J* = 11.0, 11.0, 4.5 Hz), 3.78 (3H, s), 3.04 (1H, ddd, *J* = 3.0, 3.0, 3.0 Hz), 2.78 (1H, dd, *J* = 17.9, 7.1 Hz), 2.23-2.19 (1H, m), 2.12-1.97 (4H, m), 1.90-1.77 (3H, m), 1.68 (1H, ddd, *J* = 13.1, 3.3, 3.3 Hz), 1.44 (1H, dd, *J* = 12.1, 9.3 Hz), 1.10 (3H, s), 1.08 (3H, d, *J* = 6.8 Hz), 0.94 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (600 MHz, $CDCl_3$) δ 208.8, 172.3, 162.3, 149.0, 136.1, 134.4, 129.6, 122.7, 122.6, 80.8, 66.1, 60.2, 53.0, 49.6, 46.9, 39.2, 37.2, 36.7, 36.5, 34.9, 29.9, 27.6, 26.7, 21.4, 15.5, 15.2, 14.7; IR (neat) ν_{max} 3103, 2954, 2923, 2851, 1729, 1702, 1629, 1546, 1459, 1344, 1276, 1168, 721 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{30}N_2O_9Na$: 537.1844, found: 537.1846; $[\alpha]_D^{25}$ = 5.0 (c = 0.06, $CHCl_3$).

24' (minor): R_f = 0.61 (hexane/ethyl acetate = 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (1H, dd, *J* = 2.0, 2.0 Hz), 9.16 (2H, d, *J* = 2.0 Hz), 5.75 (1H, d, *J* = 10.0 Hz), 5.64 (1H, ddd, *J* = 10.0, 4.7, 2.6 Hz), 4.85 (1H, ddd, *J* = 10.9, 10.9, 4.9 Hz), 3.72 (3H, s), 2.89 (1H, s), 2.69 (1H, dd, *J* = 18.3, 4.9 Hz), 2.57-2.49 (1H, m), 2.34 (1H, dd, *J* = 14.0, 6.1 Hz), 2.30 (1H, dd, *J* = 16.8, 12.8 Hz), 2.11 (1H, ddd, *J* = 12.8, 8.4, 4.0 Hz), 2.03 (1H, ddd, *J* = 13.6, 4.0, 4.0 Hz), 1.92-1.71 (3H, m), 1.52 (1H, dd, *J* = 13.6, 4.0 Hz), 1.32 (1H, dd, *J* = 13.6, 10.6 Hz), 1.04 (3H, d, *J* = 7.2 Hz), 1.01 (3H, s), 0.95 (3H, d, *J* = 6.1 Hz); ^{13}C NMR (600 MHz, $CDCl_3$) δ 210.6, 172.9, 162.4, 149.0, 135.2, 134.3, 129.6, 123.7, 122.6, 80.3, 60.7, 52.9, 47.2, 41.3, 40.0, 39.0, 37.4, 35.1, 34.7, 30.0, 27.0, 27.0, 21.6, 21.2, 15.5; IR (neat) ν_{max} 3102, 2926, 2853, 1726, 1628, 1545, 1344, 1271, 703 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{30}N_2O_9Na$: 537.1844, found: 537.1846; $[\alpha]_D^{25}$ = -16 (c = 0.06, $CHCl_3$).

methyl (1*S*,2*S*,4a*S*,4b*R*,10a*S*)-8-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,4a,7-trimethyl-9-oxo-2-((triisopropylsilyl)oxy)-1,3,4,4a,4b,7,8,9,10,10a-decahydrophenanthrene-8a(*2H*)-carboxylate (25)



To a stirred solution of **15a** (45.2 mg, 0.0902 mmol) and stannane **16b** (98.8 mg, 0.180 mmol, 2.0 equiv) in THF (1.5 mL) were added $Pd_2(dba)_3$ (8.3 mg, 0.0090 mmol, 0.1 equiv), $AsPh_3$ (8.3 mg, 0.0271 mmol, 0.3 equiv) and CuTC (51.6 mg, 0.271 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 12 h. Then the mixture was stirred for 12 h at 50 °C. After stirring, the reaction mixture was filtered through a plug of Celite®, and evaporated. The residue was purified

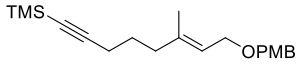
by PTLC (hexane/ethyl acetate = 8/1×2) to afford the product **25** (9.8 mg, 17%) as a colorless oil: R_f = 0.79 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (1H, d, *J* = 11.3 Hz), 5.58 (1H, ddd, *J* = 10.2, 5.7, 2.3 Hz), 3.65 (3H, s), 3.54-3.47 (1H, m), 3.42-3.29 (2H, m), 2.80 (1H, d, *J* = 5.7 Hz), 2.53-2.27 (4H, m), 2.13-1.96 (2H, m), 1.91-1.79 (2H, m), 1.70-1.18 (7H, m), 1.08 (27H, s), 0.97 (3H, d, *J* = 6.2 Hz), 0.88 (12H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 210.2, 172.3, 136.6, 122.8, 77.3, 65.9, 62.7, 53.0, 51.9, 49.4, 39.7, 39.5, 37.2, 37.0, 36.3, 36.3, 34.2, 30.9, 26.0, 20.0, 18.4, 18.3, 18.2, 15.4, 15.2, 12.9; IR (neat) ν_{max} 2926, 2855, 1743, 1702, 1460, 1102, 884, 836, 811, 777, 679 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{48}NaO_3Si$: 657.4341, found: 657.4340; $[\alpha]_D^{25}$ = -35 (c = 0.03, $CHCl_3$).

第3章

General Procedure: Gold(I)-catalyzed 1,6-ene-yne cycloisomerization

To a suspension of silver(I) bis(trifluoromethanesulfonyl)imide (5 mol %) in CH_2Cl_2 was added (triphenylphosphine)gold(I) chloride (5 mol %) in CH_2Cl_2 (0.5 mL). After stirring at room temperature for 10 min, to the solution was added starting material in CH_2Cl_2 and stirred. After disappearance of the starting material, the reaction mixture was evaporated. The residue was purified by flash chromatography to afford the product.

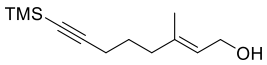
((*E*)-8-(4-methoxybenzyloxy)-6-methyloct-6-en-1-ynyl)trimethylsilane (33)



To a solution of trimethylsilyl acetylene (0.13 mL, 0.962 mmol, 1.3 equiv) and HMPA (0.65 mL, 3.70 mmol, 5.0 equiv) in THF (7 mL) was added *n*BuLi (1.64M in *n*-hexane, 0.55 mL, 0.888 mmol, 1.2 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. To the stirred solution was added **32** (232 mg, 0.740 mmol) in THF (10 mL×3) and stirred for 30 min at –78 °C and warmded to rt. After 12 h, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 80/1) to afford the product **33** (202 mg, 83%) as colorless oil:

R_f = 0.38 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.2 Hz), 6.88 (2H, d, *J* = 8.2 Hz), 5.40 (1H, t, *J* = 6.4 Hz), 4.43 (2H, s), 3.99 (2H, d, *J* = 6.4 Hz), 3.81 (3H, s), 2.24-2.07 (4H, m), 1.70-1.60 (5H, m), 0.15 (9H, s).

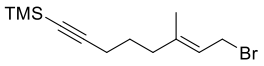
(*E*)-3-methyl-8-(trimethylsilyl)oct-2-en-7-yn-1-ol (33a)



To a solution of **33** (428 mg, 1.29 mmol) in CH_2Cl_2/H_2O (15 mL/1.5 mL, 10/1) was DDQ (441 mg, 1.94 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford the product **33a** (228 mg, 84%) as colorless oil:

R_f = 0.32 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (1H, t, *J* = 6.9 Hz), 4.15 (2H, d, *J* = 6.9 Hz), 2.21 (2H, t, *J* = 6.9 Hz), 2.11 (2H, t, *J* = 7.8 Hz), 1.70-1.60 (5H, m), 0.14 (9H, s).

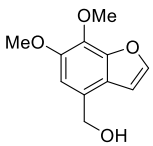
((*E*)-8-bromo-6-methyloct-6-en-1-ynyl)trimethylsilane (29)



To a stirred solution of **33a** (222 mg, 1.05 mmol) and triphenylphosphine (341 mg, 1.30 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added carbon tetrabromide (431 mg, 1.30 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 10 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **29** (161 mg, 56%) as colorless oil:

R_f = 0.58 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (1H, t, *J* = 8.3 Hz), 4.02 (2H, d, *J* = 8.3 Hz), 2.20 (2H, t, *J* = 7.3 Hz), 2.14 (2H, t, *J* = 7.3 Hz), 1.72 (3H, s), 1.65 (2H, tt, *J* = 7.3, 7.3 Hz), 0.15 (9H, s).

(6,7-dimethoxybenzofuran-4-yl)methanol (34)

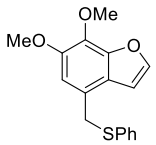


To a solution of **31** (46.7 mg, 0.227 mmol) in MeOH (1 mL) was added sodium borohydride (17.1 mg, 0.453 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 20 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **34** (40.2 mg, 85%) as colorless

oil:

R_f = 0.34 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 1.8 Hz), 6.95 (1H, s), 6.83 (1H, d, *J* = 1.8 Hz), 4.86 (2H, s), 4.15 (3H, s), 3.93 (3H, s), 1.66 (1H, br).

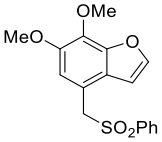
6,7-dimethoxy-4-((phenylthio)methyl)benzofuran (34a)



To a solution of **34** (48.6 mg, 0.233 mmol) and diphenyl disulfide (153mg, 0.700 mmol, 3.0 equiv.) in THF (2 mL) was added tributylphosphine (0.19 mL, 0.700 mmol, 3.0 equiv, and the reaction mixture was stirred for 1.5 h at room temperature. After disappearance of the starting material, to the reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 200/1 to 10/1) to afford the product **34a** (65.0 mg, 93%) as white amorphous:

R_f = 0.54 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 2.3 Hz), 7.35-7.18 (5H, m), 6.74 (1H, d, *J* = 2.3 Hz), 6.73 (1H, s), 4.26 (2H, s), 4.14 (3H, s), 3.82 (3H, s).

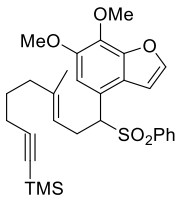
6,7-dimethoxy-4-((phenylsulfonyl)methyl)benzofuran (30)



To a solution of **34a** (97.5 mg, 0.325 mmol) in CH_2Cl_2 (5 mL) was *m*CPBA (164 mg, 0.714 mmol, 2.2 equiv) at 0 ℃, and the reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford the product **30** (103 mg, 96%) as white solid:

R_f = 0.32 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.54 (3H, m), 7.47 (1H, d, *J* = 2.3 Hz), 7.44 (2H, dd, *J* =8.2, 8.2 Hz), 6.51 (1H, s), 6.48 (1H, d, *J* = 2.3 Hz), 4.47 (2H, s), 4.17 (3H, s), 3.74 (3H, s) ; LRMS-ESI $[M+Na]^+$ calculated for $C_{17}H_{16}NaO_5S$: 355.1, found: 355.1.

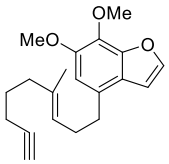
((*E*)-9-(6,7-dimethoxybenzofuran-4-yl)-6-methyl-9-(phenylsulfonyl)non-6-en-1-ynyl)trimethylsilane (35)



To a solution of **30** (122 mg, 0.367 mmol), TBAI (13.6 mg, 0.0367 mmol, 0.1 equiv) and HMPA (0.64 mL, 3.67 mmol, 10 equiv) in THF (3 mL) was added *n*BuLi (1.64M in *n*-hexane, 0.25 mL, 0.404 mmol, 1.1 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. To the stirred solution was added **29** (150 mg, 0.550 mmol, 1.5 equiv) in THF (1 mL×3) and stirred for 30 min at –78 °C and warmded to rt. After 16 h, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (5 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **35** (159 mg, 83%) as white amorphous:

R_f = 0.57 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.45 (3H, m), 7.41 (1H, d, *J* = 2.3 Hz), 7.32 (2H, dd, *J* = 8.3, 8.3 Hz), 6.74 (1H, br), 6.49 (1H, br), 4.85 (1H, t, *J* = 7.8 Hz), 4.27 (1H, dd, *J* = 11.5, 3.7 Hz), 4.15 (3H, s), 3.81 (3H, s), 3.28-3.16 (1H, m), 3.02-2.88 (1H, m), 1.93-1.84 (4H, m), 1.55 (3H, s), 1.46-1.84 (2H, m), 0.09 (9H, s).

6,7-dimethoxy-4-((*E*)-4-methylnon-3-en-8-ynyl)benzofuran (27a)



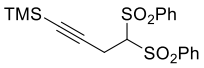
To a solution of **35** (6.7 mg, 0.0128 mmol) in MeOH (1 mL) was added magnesium turnings (1.6 mg, 0.0638 mmol, 5.0 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C and warm to rt. After 3 h stirring, to the mixture was added saturated 1M HCl solution (2 mL) and stirred until consumption of magnesium. The aqueous layer was extracted with EtOAc (10 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated, which was used next step without further purification.

To a crude solution in THF (1 mL) was added tetrabutylammonium fluoride (0.026 mL, 0.0256 mmol, 2.0 equiv) was added, and the reaction mixture was stirred for 1h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (1 mL). The aqueous layer was extracted with Et_2O (3 mL×3), and the combined organic

layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford the product **27a** as colorless oil quantitatively:

R_f = 0.53 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 2.3 Hz), 6.72 (1H, d, *J* = 2.3 Hz), 6.72 (1H, s), 5.22 (1H, t, *J* = 7.3 Hz), 4.11 (3H, s), 3.92 (3H, s), 2.79 (2H, t, *J* = 7.3 Hz), 2.36 (2H, dt, *J* = 7.3, 7.3 Hz), 2.11 (2H, dt, *J* = 7.3, 2.8 Hz), 2.06 (2H, t, *J* = 7.3 Hz), 1.95 (1H, t, *J* = 2.8 Hz), 1.60 (2H, tt, *J* = 7.3, 7.3 Hz), 1.53 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 146.9, 144.0, 134.9, 132.9, 128.7, 124.2, 122.4, 109.7, 105.1, 84.5, 68.2, 60.9, 57.4, 38.4, 33.2, 29.2, 26.6, 17.8, 15.8; IR (neat) ν_{max} 3296, 2932, 2849, 2362, 1618, 1506, 1315, 1238, 1124, 1044, 975, 632 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{20}H_{24}NaO_3$: 335.1618, found: 335.1617.

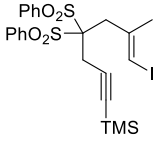
(4,4-bis(phenylsulfonyl)but-1-yn-1-yl)trimethylsilane (40)



To a stirred suspension of sodium hydride (618 mg, 15.5 mmol, 1.0 equiv) and tetrabutylammonium iodide (0.5708 g, 1.55 mmol, 0.1 equiv) in DMF (15 mL) was added bis(phenylsulfonyl)methane (**38**) (4.58 g, 15.5 mmol, 1.0 equiv) in DMF (15 mL) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, 3-bromo-1-trimethylsilylprop-1-yne(**39**) (3.2495 g, 17.0 mmol, 1.1 equiv) in DMF (3 mL) was added and stirred. After 2 h at room temperature, to the reaction mixture was added saturated aqueous NH_4Cl solution (30mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **40** (3.26 g, 52%) as a white powder:

R_f = 0.25 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (4H, d, *J* = 8.3 Hz), 7.72 (2H, dd, *J* = 8.3, 8.3 Hz), 7.59 (4H, dd, *J* = 8.3, 8.3 Hz), 4.59 (1H, t, *J* = 6 Hz), 3.17 (2H, d, *J* = 6.0 Hz), 0.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 134.8, 129.8, 129.1, 98.5, 89.1, 82.3, 17.9, -0.3; IR (neat) ν_{max} 3066, 2957, 2183, 1584, 1448, 1323, 1312, 1078, 998, 841, 756, 685, 573 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{19}H_{22}NaO_4S_2Si$: 429.0621, found: 429.0620; mp 83.9 – 84.8 °C.

(*E*)-(7-iodo-6-methyl-4,4-bis(phenylsulfonyl)hept-6-en-1-yn-1-yl)trimethylsilane (36)

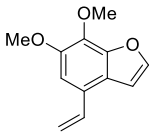


To a stirred suspension of sodium hydride (22.6 mg, 0.565 mmol, 1.1 equiv) in DMF (3 mL) was added **40** (208.8 mg, 0.512 mmol) in DMF (1 mL) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, (*E*)-3-bromo-1-iodo-2-methylprop-1-ene (**41**) (0.1608 g,

0.616 mmol, 1.2 equiv) in DMF (1 mL) was added, and stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (100 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **36** (0.181 g, 77%) as a white powder:

R_f = 0.58 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (4H, d, *J* = 7.8 Hz), 7.70 (2H, dd, *J* = 7.8, 7.8 Hz), 7.55 (4H, dd, *J* = 7.8, 7.8 Hz), 6.51 (1H, s), 3.37 (2H, s), 3.35 (2H, s), 1.98 (3H, s), 0.07 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 137.1, 134.8, 131.7, 128.6, 98.3, 93.1, 89.4, 85.2, 37.7, 25.1, 23.6, -0.3; IR (neat) ν_{max} 3064, 2958, 2897, 1446, 1331, 1313, 1297, 1274, 1250, 1145, 1076, 842, 727, 685, 580 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{23}H_{27}INaO_4S_2Si$: 609.0057, found: 609.0055; mp 125.2 – 128.0 °C.

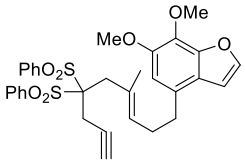
6,7-dimethoxy-4-vinylbenzofuran (37)



To a stirred solution of $MePPh_3Br$ (2.14 g, 5.99 mmol, 1.2 equiv) in THF (30 mL) was added *n*BuLi (1.55M in *n*-hexane, 3.54 mL, 5.49 mmol, 1.1 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, **31** (1.03 g, 5.00 mmol) in THF (5×3mL) was added, and stirred for 3 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **37** (0.897 g, 88%) as colorless oil:

R_f = 0.56 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 2.3 Hz), 7.02 (1H, s), 6.91 (1H, dd, *J* = 17.8, 11.5 Hz), 6.88 (1H, d, *J* = 2.3 Hz), 5.76 (1H, d, *J* = 17.8 Hz), 5.34 (1H, d, *J* = 11.5 Hz), 4.17 (3H, s), 3.94 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 146.9, 144.7, 134.6, 133.9, 124.1, 121.9, 114.2, 106.8, 105.1, 60.9, 57.3; IR (neat) ν_{max} 2935, 2838, 2365, 1609, 1541, 1294, 1127, 1076, 737, 590 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{12}H_{12}NaO_3$: 227.0679, found: 227.0679.

(*E*)-6,7-dimethoxy-4-(4-methyl-6,6-bis(phenylsulfonyl)non-3-en-8-yn-1-yl)benzofuran (27b)

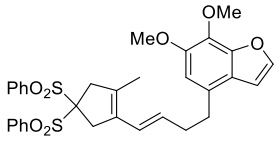


To a stirred solution of **37** (93.0 mg, 0.455 mmol) in THF (4.0 mL) was added 9-BBN (0.5M in THF, 1.36 mL, 0.683 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added H_2O (0.4 mL) at 0 °C and stirred further 30 min. After addition of vinyl iodide **36** (534 mg, 0.911 mmol, 2.0 equiv) in THF (4.0 mL) , $PdCl_2(dppf)\cdot CH_2Cl_2$ (37.1 mg, 0.0455 mmol, 10 mol %) and Tl_2CO_3 (426 mg, 0.911 mmol, 2.0 equiv), the resulting mixture was stirred for 24 h at reflux temperature. Then, to the mixture was added saturated $NaHCO_3$ solution (20 mL) and filtered through Celite® pad. Then the aqueous layer was extracted with EtOAc (10 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

To a stirred solution of crude material in THF/EtOH/H_2O (2 mL/2 mL/0.5mL) was added silver nitrate (116 mg, 0.683 mmol, 1.5 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, thee reaction mixture was added KI (128 mg, 0.744 mmol, 1.7 equiv) and stirred. After 2 h, the suspension was filtered through Celite® pad and washed with EtOAc (30 mL). The filtrate was washed with saturated aqueous NH_4Cl solution (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 6/1) to afford the product **27b** (53.9 mg, 20%) as beige solid:

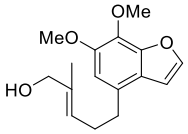
R_f = 0.32 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (4H, d, *J* = 7.9 Hz), 7.67 (2H, dd, *J* = 7.9, 7.9 Hz), 7.54 (1H, d, *J* = 2.3 Hz), 7.52 (4H, dd, *J* = 7.9 Hz), 6.74 (1H, s), 6.72 (1H, d, *J* = 2.3 Hz), 5.60 (1H, t, *J* = 7.4 Hz), 4.12 (3H, s), 3.91 (3H, s), 3.29 (2H, d, *J* = 2.8 Hz), 3.10 (2H, s), 2.83 (2H, t, *J* = 7.4 Hz), 2.41 (2H, dt, *J* = 7.4, 7.4 Hz), 1.97 (1H, t, *J* = 2.8 Hz), 1.77 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.1, 137.4, 134.7, 133.0, 132.8, 131.7, 128.5, 128.3, 128.2, 122.4, 109.8, 105.1, 90.1, 77.1, 75.3, 61.0, 57.4, 38.7, 32.4, 29.5, 22.4, 17.4; IR (neat) ν_{max} 3272, 2934, 2254, 1505, 1310, 1238, 1142, 1076, 910, 727, 686, 578 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{32}H_{32}NaO_7S_2$: 615.1482, found: 615.1480; mp 58.2 – 62.4 °C.

(*E*)-6,7-dimethoxy-4-(4-(2-methyl-4,4-bis(phenylsulfonyl)cyclopent-1-en-1-yl)but-3-en-1-yl)ben zofuran (28b')



According to *general procedure*, **28b'** was obtained as colorless amorphous (quantitative yield): R_f = 0.74 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (4H, d, *J* = 8.0 Hz), 7.66 (2H, dd, *J* = 8.0 Hz), 7.58 (1H, d, *J* = 2.3 Hz), 7.50 (4H, dd, *J* = 8.0 Hz), 6.72 (1H, s), 6.72 (1H, d, *J* = 2.3 Hz), 5.87 (1H, d, *J* = 16.0 Hz), 5.49 (1H, dt, *J* = 16.0, 7.5 Hz), 4.13 (3H, s), 3.92 (3H, s), 3.40 (2H, s), 3.26 (2H, s), 2.85 (2H, t, *J* = 7.5 Hz), 2.44 (2H, dt, *J* = 7.5, 7.5 Hz), 1.35 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.1, 137.4, 134.7, 133.0, 132.8, 131.7, 128.5, 128.3, 128.2, 122.4, 109.8, 105.1, 90.1, 77.1, 75.3, 61.0, 57.4, 38.7, 32.4, 29.5, 22.4, 17.5; IR (neat) ν_{max} 2932, 1508, 1447, 1328, 1311, 1145, 1125, 1078, 755, 725, 689, 553 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{32}H_{32}NaO_7S_2$: 615.1482, found: 615.1481.

(*E*)-5-(6,7-dimethoxybenzofuran-4-yl)-2-methylpent-2-en-1-ol (43)



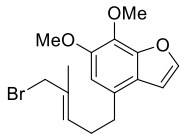
To a stirred solution of **37** (865 mg, 4.23 mmol) in THF (40 mL) was added 9-BBN (0.5M in THF, 12.7 mL, 6.35 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added H_2O (5.0 mL) at 0 °C and stirred further 30 min. After addition of vinyl iodide **42** (2.64 g, 8.46 mmol, 2.0 equiv) in THF (20 mL), $PdCl_2(dppf)\cdot CH_2Cl_2$ (345 mg, 0.423 mmol, 10 mol %) and $Ba(OH)_2\cdot 8H_2O$ (2.67 g, 8.46 mmol, 2.0 equiv), the resulting mixture was stirred for 24 h at room temperature. Then, to the mixture was added saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with EtOAc (30 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

To a stirred solution of crude material in THF (50 mL) was added tetrabutylammonium fluoride (1.0M in THF, 21.2 mL, 21.2 mmol, 5.0 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with EtOAc (30 mL×3), and the combined organic layer was washed with H_2O (30 mL), brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **43** (642 mg, 55%) as colorless oil:

R_f = 0.25 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 2.3 Hz), 6.73

(1H, s), 6.71 (1H, d, J = 2.3 Hz), 5.49 (1H, t, J = 7.4 Hz), 4.11 (3H, s), 3.99 (2H, s), 3.91 (3H, s), 2.82 (2H, t, J = 7.4 Hz), 2.41 (2H, dt, J = 7.4, 7.4 Hz), 1.80 (1H, br), 1.60 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.1, 135.6, 133.1, 128.4, 125.0, 122.5, 109.8, 105.1, 68.8, 61.0, 57.5, 32.9, 28.9, 13.6; IR (neat) ν_{max} 3374, 2932, 2849, 1618, 1504, 1121, 1041, 735, 593 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{16}H_{20}NaO_4$: 299.1254, found: 299.12553.

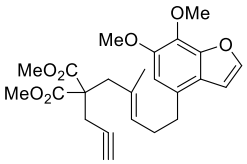
(*E*)-4-(5-bromo-4-methylpent-3-en-1-yl)-6,7-dimethoxybenzofuran (44)



To a stirred solution of **43** (612 mg, 2.21 mmol) and triphenylphosphine (695 mg, 2.65 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL) was added carbon tetrabromide (879 mg, 2.65 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford the product **44** (720 mg, 96%) as colorless oil:

R_f = 0.42 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 2.3 Hz), 6.71 (1H, s), 6.70 (1H, d, J = 2.3 Hz), 5.65 (1H, t, J = 7.5 Hz), 4.11 (3H, s), 3.94 (2H, s), 3.92 (3H, s), 2.82 (2H, t, J = 7.5 Hz), 2.41 (2H, dt, J = 7.5, 7.5 Hz), 1.69 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.2, 133.1, 132.9, 130.2, 127.8, 122.4, 109.8, 105.0, 61.0, 57.4, 41.4, 32.4, 29.4, 14.6; IR (neat) ν_{max} 2933, 2838, 1618, 1542, 1504, 1446, 1222, 1041, 736, 603 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{16}H_{19}BrNaO_3$: 361.0410, found: 361.0410.

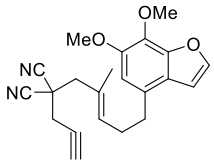
dimethyl
(*E*)-2-(5-(6,7-dimethoxybenzofuran-4-yl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (27c)



To a solution of **44** (102 mg, 0.301 mmol, 1.2 equiv), malonate **45** (42.7 mg, 0.251mmol, 1.0 equiv) and tetrabutylammonium iodide (9.2 mg, 0.0251 mmol, 0.1 equiv) in acetone (3.0 mL) was added cesium carbonate (89.9 g, 0.276 mmol, 1.1 equiv) and stirred for 20 h at reflux temperature. Then, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (5 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **27c** (50.5 mg, 47%) as colorless oil:

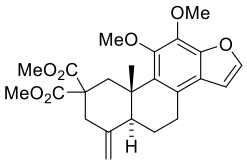
R_f = 0.46 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 2.3 Hz), 6.72 (1H, s), 6.71 (1H, d, *J* = 2.3 Hz), 5.38 (1H, t, *J* = 7.4 Hz), 4.11 (3H, s), 3.92 (3H, s), 3.70 (6H, s), 2.79 (2H, t, *J* = 7.4 Hz), 2.78 (2H, s), 2.72 (2H, d, *J* = 2.3 Hz), 2.37 (2H, dt, *J* = 7.4, 7.4 Hz), 2.01 (1H, t, *J* = 2.3 Hz), 1.46 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 148.6, 147.0, 144.0, 133.0, 130.1, 129.9, 128.3, 122.3, 109.7, 105.1, 79.2, 71.6, 60.9, 57.3, 56.6, 52.6, 41.4, 32.8, 29.2, 22.4, 16.7; IR (neat) ν_{max} 3283, 2953, 2844, 1736, 1507, 1438, 1324, 1214, 1124, 1044, 976, 657 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{24}H_{28}NaO_7$: 451.1727, found: 451.1728.

(*E*)-2-(5-(6,7-dimethoxybenzofuran-4-yl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malononitrile (27d)



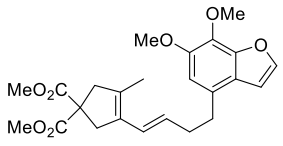
To a solution of **44** (106 mg, 0.312 mmol, 1.2 equiv), malononitrile **46** (27.1 mg, 0.260 mmol, 1.0 equiv) and tetrabutylammonium iodide (9.6 mg, 0.0260 mmol, 0.1 equiv) in MeCN (3.0 mL) was added cesium carbonate (93.2 mg, 0.286 mmol, 1.1equiv) and stirred for 20 h at 80 °C. Then, to the reaction mixture was cooled to room temperature and added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (5 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **27d** (37.7 mg, 40%) as colorless oil:
R_f = 0.43 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz), 6.74 (1H, s), 6.72 (1H, d, *J* = 2.3 Hz), 5.61 (1H, t, *J* = 7.4), 4.12 (3H, s), 3.92 (3H, s), 2.87 (2H, t, *J* = 7.4 Hz), 2.82 (2H, d, *J* = 2.8 Hz), 2.70 (2H, s), 2.48 (2H, dt, *J* = 7.4, 7.4 Hz), 2.39 (1H, t, *J* = 2.8 Hz), 1.78 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.2, 133.5, 133.2, 127.7, 127.4, 122.3, 114.7, 109.9, 104.9, 75.4, 74.6, 60.9, 57.4, 45.5, 36.3, 32.4, 29.3, 28.3, 17.1; IR (neat) ν_{max} 3287, 2933, 2846, 1618, 1543, 1505, 1447, 1315, 1238, 1123, 1076, 1041, 973, 869, 844, 736, 648 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{22}H_{22}N_2NaO_3$: 385.1523, found: 385.1525.

dimethyl (5a*S,9a*S**)-10,11-dimethoxy-9a-methyl-6-methylene-5,5a,6,7,9,9a-hexahydrophenanthro[2,1-b]furan-8,8(4*H*)-dicarboxylate (28c)**



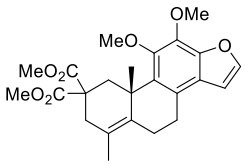
dimethyl

(*E*)-3-(4-(6,7-dimethoxybenzofuran-4-yl)but-1-en-1-yl)-4-methylcyclopent-3-ene-1,1-dicarboxylate (28c')



dimethyl

(*S)-10,11-dimethoxy-6,9a-dimethyl-5,7,9,9a-tetrahydrophenanthro[2,1-b]furan-8,8(4*H*)-dicarboxylate (28c'')**



According to general procedure, **28c** and **28c''** were obtained as colorless oil (9.2 mg, 30%, ratio of **28c**:**28c''** = 1:3) and **28c'** was obtained (17.3 mg, 57%) as colorless oil:

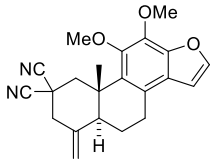
28c and **28c''**: R_f = 0.60 (hexane/ethyl acetate = 2/1); IR (neat) ν_{max} 2917, 2848, 1735, 1473, 1432, 1333, 1237, 1145, 1114, 1059, 994, 902, 749 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{24}H_{28}NaO_7$: 451.1727, found: 451.1728.

28c: ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 2.3 Hz), 6.69 (1H, d, *J* = 2.3 Hz), 5.16 (1H, br), 4.80 (1H, br), 4.10 (3H, s), 3.96 (3H, s), 3.78 (3H, s), 3.69 (3H, s), 3.24 (1H, d, *J* = 13.7 Hz), 3.08-2.80 (2H, m), 2.33 (1H, d, *J* = 13.7 Hz), 2.28 (1H, d, *J* = 13.7 Hz), 2.08 (1H, d, *J* = 13.7 Hz), 1.93-1.67 (3H, m), 1.05 (3H, s); ^{13}C NMR (125 MHz, CDCl3) δ 172.7, 172.5, 149.1, 145.3, 145.2, 144.3, 137.1, 134.3, 123.7, 122.5, 110.8, 105.4, 61.1, 60.6, 55.3, 52.8, 52.3, 50.3, 40.5, 40.1, 29.7, 28.0, 20.4, 19.0;

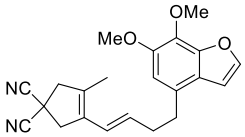
28c'': ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz), 6.70 (1H, d, *J* = 2.3 Hz), 4.08 (3H, s), 3.74 (3H, s), 3.71 (3H, s), 3.63 (3H, s), 3.04 (1H, d, *J* = 16.0 Hz), 2.96-2.69 (3H, m), 2.58 (1H, d, *J* = 16.0 Hz), 1.96-1.69 (3H, m), 1.57 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.6, 147.3, 145.3, 144.1, 136.6, 136.2, 127.5, 127.3, 124.0, 123.6, 105.1, 60.6, 60.5, 57.2, 52.6, 52.6, 46.2, 43.9, 32.8, 29.2, 26.2, 19.7, 13.4;

28c': R_f = 0.46 (hexane/ethyl acetate = 2/1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 2.3 Hz), 6.73 (1H, s), 6.71 (1H, d, *J* = 2.3 Hz), 6.27 (1H, d, *J* = 15.6 Hz), 5.58 (1H, dt, *J* = 15.6, 7.3 Hz), 4.12 (3H, s), 3.91 (3H, s), 3.74 (6H, s), 3.10 (2H, s), 3.04 (2H, s), 2.86 (2H, t, *J* = 7.3 Hz), 2.48 (2H, dt, *J* = 7.3 Hz), 1.73 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 148.6, 147.0, 144.1, 133.0, 132.4, 130.5, 130.0, 128.2, 124.2, 122.4, 109.8, 105.2, 61.0, 57.4, 57.0, 52.8, 46.4, 41.2, 34.4, 33.3, 13.4; IR (neat) ν_{max} 2952, 2847, 1733, 1618, 1543, 1507, 1436, 1397, 1259, 1124, 1075, 1044, 972, 871, 740 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{24}H_{28}NaO_7$: 451.1727, found: 451.1729.

(5a*S,9a*S**)-10,11-dimethoxy-9a-methyl-6-methylene-5,5a,6,7,9,9a-hexahydrophenanthro[2,1-b]furan-8,8(4*H*)-dicarbonitrile (28d)**



(E)-3-(4-(6,7-dimethoxybenzofuran-4-yl)but-1-en-1-yl)-4-methylcyclopent-3-ene-1,1-dicarbonitrile (28d')

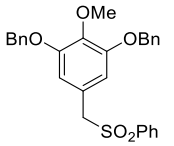


According to *general procedure*, **28d** was obtained as colorless oil (87%) and trace amount of **28d'** was obtained:

28d: R_f = 0.60 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 2.3 Hz), 6.69 (1H, d, *J* = 2.3 Hz), 5.33 (1H, br), 5.04 (1H, br), 4.13 (3H, s), 4.03 (1H, dd, *J* = 12.6, 1.7 Hz), 3.97 (3H, s), 3.07 (1H, dd, *J* = 12.6, 1.7 Hz), 3.05-2.89 (2H, m), 2.74 (1H, d, *J* = 12.6 Hz), 2.27 (1H, d, *J* = 12.6 Hz), 2.03 (1H, d, *J* = 12.6 Hz), 1.93 (1H, dd, *J* = 6.9, 6.3 Hz), 1.82 (1H, dddd, *J* = 12.6, 12.6, 12.6, 6.3 Hz), 1.45 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 145.4, 144.7, 140.9, 137.1, 132.7, 124.0, 121.8, 116.8, 116.7, 114.8, 105.3, 61.3, 60.7, 49.6, 44.3, 43.6, 40.7, 32.4, 27.6, 20.6, 20.3; IR (neat) ν_{max} 2989, 2943, 2842, 1604, 1473, 1397, 1332, 1143, 1056, 912, 878, 748 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{22}H_{22}N_2NaO_3$: 385.1523, found: 385.1523.

28d': R_f = 0.50 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz), 6.72 (1H, s), 6.70 (1H, d, *J* = 2.3 Hz), 6.26 (1H, d, *J* = 16.0 Hz), 5.58 (2H, dt, *J* = 16.0, 7.3 Hz), 4.13 (3H, s), 3.92 (3H, s), 3.24 (2H, s), 3.20 (2H, s), 2.88 (2H, t, *J* = 7.3 Hz), 2.53 (2H, dt, *J* = 7.3, 7.3 Hz), 1.80 (3H, s) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.0, 144.3, 133.2, 132.7, 130.7, 130.3, 127.5, 123.0, 122.5, 116.9, 109.8, 105.0, 61.0, 57.5, 50.0, 45.4, 34.4, 33.0, 30.5, 13.3; IR (neat) ν_{max} 2935, 2850, 1718, 1508, 1458, 1313, 1124, 1077, 969, 747, 544 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{22}H_{22}N_2NaO_3$: 385.1523, found: 385.1523.

(((2-methoxy-5-((phenylsulfonyl)methyl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (50)

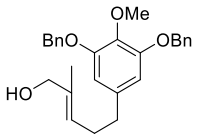


To a stirred solution of known benzyl bromide **49** (20.4 g, 49.4 mmol) in DMF (250 mL) was added

sodium benzenesulfinate (9.72 g, 59.2 mmol, 1.2 equiv) and the reaction mixture was stirred for 16 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (300 mL). The aqueous layer was extracted with EtOAc (100 mL×3), and the combined organic layer was washed with H_2O (150 mL×3), dried over Na_2SO_4, and evaporated to form white solid. The residue was collected and washed with hexane (100 mL×3) to afford the product **50** (18.5 g, 79%) as white solid, which was used a next step without further purification:

R_f = 0.48 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.55 (3H, m), 7.45-7.29 (12H, m), 6.34 (2H, s), 4.95 (4H, s), 4.17 (2H, s), 3.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 140.0, 137.8, 136.7, 133.6, 128.8, 128.7, 128.5, 127.9, 127.2, 123.2, 110.5, 71.1, 62.9, 61.0; IR (neat) ν_{max} 3062, 3031, 2928, 2829, 1979, 1591, 1504, 1438, 1307, 1249, 1152, 1105, 1086, 1027, 1002, 839, 739, 696, 626 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{26}NaO_5S$: 497.1393, found: 497.1394; mp: 151.4-152.1 °C.

(*E*)-5-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-methylpent-2-en-1-ol (52)



To a stirred solution of **50** (9.20 g, 19.0 mmol) in THF (100 mL) and DMPU (20 mL) was added *n*BuLi (1.64M in *n*-hexane, 12.7 mL, 20.9 mmol, 1.1 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at 0 °C. Then, a stirred solution was cooled to –78 °C again, **51** (6.37 g, 22.8 mmol, 1.2 equiv) in THF (20 mL×3) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (150 mL×3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

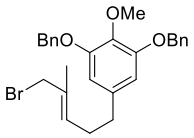
To a solution of crude material in MeOH (750 mL) was added magnesium turnings (4.61 g, 190 mmol, 10 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C and warm to rt. After 8 h stirring, to the mixture was added saturated 1M HCl solution (200 mL) and stirred until consumption of magnesium. The aqueous layer was extracted with EtOAc (150 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

To a stirred solution of crude material in THF (400 mL) was added tetrabutylammonium fluoride (1.0M in THF, 38.0 mL, 38.0 mmol, 2.0 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (150

mL×3), and the combined organic layer was washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford the product **52** (3.42 g, 43% over 3 steps) as pale-yellow oil:

R_f = 0.10 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (4H, d, *J* = 7.4 Hz), 7.37 (4H, dd, *J* = 7.4, 7.4 Hz), 7.31 (2H, dd, *J* = 7.4, 7.4 Hz) 6.45 (2H, s), 5.34 (1H, t, *J* = 7.4 Hz), 5.12 (4H, s), 3.95 (2H, s), 3.88 (3H, s), 2.53 (2H, t, *J* = 7.4 Hz), 2.25 (2H, dt, *J* = 7.4, 7.4 Hz), 1.58 (3H, s), 1.46 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 137.8, 137.6, 137.5, 135.6, 128.6, 127.9, 127.4, 125.1, 108.4, 71.3, 68.9, 61.1, 35.9, 29.5, 13.8; IR (neat) ν_{max} 3421, 3063, 3030, 2928, 2861, 1588, 1503, 1433, 1371, 1321, 1233, 1109, 1005, 826, 735, 696, 594 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{27}H_{30}NaO_4$: 441.2036, found: 441.2036.

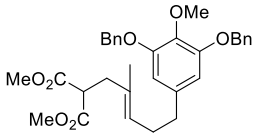
(*E*)-(((5-(5-bromo-4-methylpent-3-en-1-yl)-2-methoxy-1,3-phenylene)bis(oxy))bis(methylene)) dibenzene (53)



To a stirred solution of **52** (3.42 g, 8.17 mmol) and triphenylphosphine (2.57 g, 9.81 mmol, 1.2 equiv) in CH_2Cl_2 (100 mL) was added carbon tetrabromide (3.25 g, 9.81 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford the product **53** (3.77 g, 96%) as colorless oil:

R_f = 0.75 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (4H, d, *J* = 7.4 Hz), 7.38 (4H, dd, *J* = 7.4, 7.4 Hz), 7.32 (2H, dd, *J* = 7.4, 7.4 Hz), 6.44 (2H, s), 5.55 (1H, t, *J* = 7.4 Hz), 5.13 (4H, t, *J* = 7.4 Hz), 3.92 (2H, s), 3.89 (3H, s), 2.54 (2H, t, *J* = 7.4 Hz), 2.25 (2H, dt, *J* = 7.4, 7.4 Hz), 1.67 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.8, 137.3, 137.0, 132.7, 130.2, 128.5, 127.8, 127.2, 108.3, 71.1, 61.0, 41.5, 35.3, 29.9, 14.6; IR (neat) ν_{max} 3063, 3030, 2926, 2826, 1588, 1504, 1434, 1370, 1235, 1121, 1009, 906, 826, 736, 696, 604 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{27}H_{29}BrNaO_3$: 503.1192, found: 503.1195.

dimethyl (*E*)-2-(5-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-methylpent-2-en-1-yl)malonate (54)

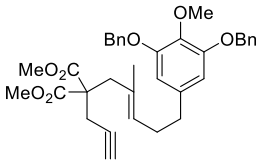


To a stirred suspension of sodium hydride (898 mg, 2.24 mmol, 1.1 equiv) in THF (20 mL) was added dimethyl malonate (0.35 mL, 3.06 mmol, 1.5 equiv) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, **53** (983 mg, 2.04 mmol) in THF (5 mL×3) was

added, and stirred for 12 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **54** (1.09 g, 94%) as colorless oil:

R_f = 0.23 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (4H, d, *J* = 7.4 Hz), 7.38 (4H, dd, *J* = 7.4, 7.4 Hz), 7.31 (2H, dd, *J* = 7.4, 7.4 Hz), 6..45 (2H, s), 5.20 (1H, t, *J* = 7.3 Hz), 5.13 (4H, s), 3.88 (3H, s), 3.70 (6H, s), 3.56 (1H, t, *J* = 7.9 Hz), 2.57 (2H, d, *J* = 7.9 Hz), 2.48 (2H, t, *J* = 7.3 Hz), 2.19 (2H, dt, *J* = 7.3, 7.3 Hz), 1.57 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 152.4, 137.7, 137.5, 137.4, 131.5, 128.5, 127.7, 127.2, 126.6, 108.2, 71.1, 60.9, 52.4, 50.6, 38.5, 35.9, 29.7, 15.7; IR (neat) ν_{max} 3031, 2950, 1733, 1587, 1504, 1433, 1371, 1340, 1232, 1149, 1103, 1009, 908, 828, 735, 697 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{32}H_{36}NaO_7$: 555.2353, found: 555.2353.

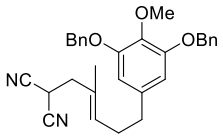
dimethyl (*E*)-2-(5-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (47c)



To a stirred suspension of sodium hydride (998 mg, 2.50 mmol, 1.3 equiv) in THF (10 mL) was added **54** (1.09 g, 1.92 mmol) in THF (5 mL×3) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, propargyl bromide (0.22 mL, 2.88 mmol, 1.5 equiv) was added, and stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **47c** (1.12 g, 96%) as colorless oil:

R_f = 0.25 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (4H, d, *J* = 7.4 Hz), 7.37 (4H, dd, *J* = 7.4, 7.4 Hz), 7.31 (2H, dd, *J* = 7.4, 7.4 Hz), 6.46 (2H, s), 5.31 (1H, t, *J* = 7.4 Hz), 5.13 (4H, s), 3.88 (3H, s), 3.71 (6H, s), 2.78 (2H, s), 2.73 (2H, d, *J* = 2.3 Hz), 2.53 (2H, d, *J* = 7.4 Hz), 2.23 (2H, dt, *J* = 7.4, 7.4 Hz), 2.02 (1H, t, *J* = 2.3 Hz), 1.46 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 152.4, 137.7, 137.4, 137.4, 130.1, 129.8, 128.5, 127.7, 127.3, 108.2, 79.4, 71.7, 71.1, 60.9, 56.6, 52.6, 41.5, 35.7, 29.8, 22.5, 16.8; IR (neat) ν_{max} 3288, 3031, 2950, 1736, 1588, 1505, 1434, 1371, 1288, 1212, 1105, 1009, 847, 737, 698, 653 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{38}NaO_7$: 593.2510, found: 593.2509.

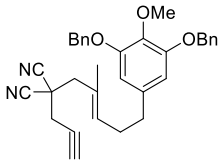
(*E*)-2-(5-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-methylpent-2-en-1-yl)malononitrile (55)



To a stirred solution of **53** (2.64g, 5.49 mmol), malononitrile (544 mg, 8.24 mmol, 1.5 equiv) and tetrabtuylammonium iodide (203 mg, 0.549 mmol, 0.1 equiv) in CH_2Cl_2 (50 mL) was added *i*Pr_2NEt (0.95 mL, 5.49 mmol, 1.0 equiv) and the reaction mixture was stirred for 24 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL×3), dried over Na_2SO_4, and evaporated. The residue was roughly purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **55** as pale-yellow oil, which was pure enough for the next reaction:

R_f = 0.16 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (4H, d, *J* = 7.4 Hz), 7.38 (4H, dd, *J* = 7.4, 7.4 Hz), 7.32 (2H, dd, *J* = 7.4, 7.4 Hz), 6.45 (2H, s), 5.41 (1H, t, *J* = 7.4 Hz), 5.14 (4H, s), 3.89 (3H, s), 3.70 (1H, t, *J* = 7.4 Hz), 2.57 (2H, t, *J* = 7.4 Hz), 2.55 (2H, t, *J* = 7.4 Hz), 2.28 (2H, dt, *J* = 7.4, 7.4 Hz), 1.59 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.8, 137.4, 136.9, 131.4, 128.5, 127.8, 127.6, 127.2, 112.4, 108.3, 71.0, 60.9, 40.3, 35.5, 29.8, 22.0, 15.6; IR (neat) ν_{max} 3064, 3032, 2917, 2828, 2254, 1588, 1504, 1433, 1371, 1340, 1319, 1233, 1178, 1101, 1004, 908, 826, 732, 696, 648, 565 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{30}H_{30}N_2NaO_3$: 489.2149, found: 489.2149.

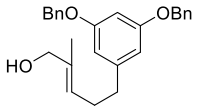
(*E*)-2-(5-(3,5-bis(benzyloxy)-4-methoxyphenyl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malononitrile (47d)



To a stirred solution of crude **55** in THF (300 mL) was added *n*BuLi (1.60M in *n*-hexane, 3.4 mL, 5.49 mmol, 1.0 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution, propargyl bromide (0.41 mL, 5.49 mmol, 1.0 equiv) in THF (20 mL×3) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **47d** (2.11 g, 76%) as colorless oil:

R_f = 0.19 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (4H, d, *J* = 7.4 Hz), 7.38 (4H, dd, *J* = 7.4, 7.4 Hz), 7.31 (2H, dd, *J* = 7.4, 7.4 Hz), 6.46 (2H, s), 5.49 (1H, t, *J* = 6.52 Hz), 5.13 (4H, s), 3.88 (3H, s), 2.79 (2H, d, *J* = 2.3 Hz), 2.65 (2H, s), 2.57 (2H, t, *J* = 7.4 Hz), 2.37 (1H, t, *J* = 2.3 Hz), 2.31 (2H, dt, *J* = 7.4, 7.4 Hz), 1.73 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.8, 137.4, 136.9, 133.5, 128.5, 127.8, 127.3, 127.2, 114.7, 108.3, 75.4, 74.7, 71.1, 61.0, 45.5, 36.3, 35.4, 29.9, 28.3, 17.2; IR (neat) ν_{max} 3263, 3032, 2926, 1587, 1505, 1432, 1372, 1341, 1322, 1235, 1179, 1103, 1004, 908, 825, 734, 696, 650 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{33}H_{32}N_2NaO_3$: 527.2305, found: 527.2307; mp: 135.3-137.3 °C.

(*E*)-5-(3,5-bis(benzyloxy)phenyl)-2-methylpent-2-en-1-ol (60)



To a stirred solution of magnesium (236 mg, 9.72 mmol, 10 equiv) in Et_2O (10 mL) was added dibromoethane (0.084 mL, 0.972 mmol, 1.0 equiv) and the reaction mixture was stirred for 1 h at room temperature. After activation of magnesium, the reaction mixture was cool to 0 °C. Then to the solution was added benzyl bromide **59** (745 mg, 1.94 mmol, 2.0 equiv) in THF (10 mL×3) and stirred until **59** was fully consumed to form Grignard reagent.

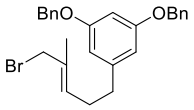
To a stirred solution of acetate **58** (251 mg, 9.72 mmol) in THF (10 mL) was added Li_2CuCl_4 (0.1M in THF, 0.97 ml, 0.0972 mmol, 0.1 equiv) then prepared Grignard reagent. The reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layer was washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was roughly purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product, which was pure enough for the next reaction.

To a stirred solution of crude material in THF (20 mL) was added tetrabutylammonium fluoride (1.0M in THF, 1.9 mL, 1.94 mmol, 2.0 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **60** (364 mg, 96% over 2 steps) as white solid:

R_f = 0.06 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (4H, d, *J* = 6.8 Hz), 7.39 (4H, dd, *J* = 6.8, 6.8 Hz), 7.33 (2H, dd, *J* = 6.8, 6.8 Hz), 6.49 (1H, dd, *J* = 2.3, 2.3 Hz), 6.47 (2H, d, *J* = 2.3 Hz), 5.45 (1H, t, *J* = 7.9 Hz), 5.03 (4H, s), 3.99 (2H, s), 2.61 (2H, t, *J* = 7.9 Hz), 2.35 (2H, dt, *J* = 7.9, 7.9 Hz), 1.64 (3H, s), 1.41 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 144.4, 136.9,

135.5, 128.6, 127.9, 127.5, 125.1, 107.7, 99.4, 70.0, 68.8, 35.9, 29.2, 13.7; IR (neat) ν_{max} 3326, 3064, 3031, 2915, 2859, 1591, 1497, 1451, 1374, 1344, 1290, 1214, 1146, 1056, 1027, 1001, 907, 827, 730, 694, 631 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{28}NaO_3$: 411.1931, found: 411.1932 mp: 59.5-60.6 °C.

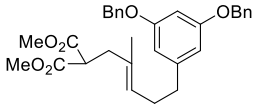
(*E*)-(((5-(5-bromo-4-methylpent-3-en-1-yl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (61)



To a stirred solution of **60** (364 mg, 0.937 mmol) and triphenylphosphine (295 mg, 1.12 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added carbon tetrabromide (373 mg, 1.12 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford the product **61** (373 mg, 88%) as colorless oil:

R_f = 0.60 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (4H, d, *J* = 7.4 Hz), 7.39 (4H, dd, *J* = 7.4, 7.4 Hz), 7.33 (2H, dd, *J* = 7.4, 7.4 Hz), 6.49 (1H, dd, *J* = 2.3, 2.3 Hz) , 6.44 (2H, d, *J* = 2.3 Hz), 5.62 (1H, t, *J* = 7.3 Hz), 5.03 (4H, s), 3.95 (2H, s), 2.61 (2H, t, *J* = 7.3 Hz), 2.33 (2H, dt, *J* = 7.3, 7.3 Hz), 1.71 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 143.9, 137.0, 132.7, 130.3, 128.6, 127.9, 127.5, 107.7, 99.6, 70.0, 41.6, 35.5, 29.8, 14.6; IR (neat) ν_{max} 3063, 3031, 2918, 2860, 1591, 1451, 1373, 1343, 1290, 1264, 1204, 1146, 1080, 1053, 827, 733, 694, 602 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{27}BrNaO_2$: 473.1087, found: 473.1089.

dimethyl (*E*)-2-(5-(3,5-bis(benzyloxy)phenyl)-2-methylpent-2-en-1-yl)malonate (61a)

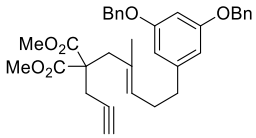


To a stirred suspension of sodium hydride (33.3 mg, 0.834 mmol, 1.1 equiv) in THF (5 mL) was added dimethyl malonate (0.13 mL, 1.14 mmol, 1.5 equiv) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, **61** (342 mg, 0.758 mmol) in THF (1 mL×3) was added, and stirred for 12 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **61a** quantitative yield as colorless oil:

R_f = 0.25 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (4H, d, *J* = 7.4 Hz), 7.38

(4H, dd, J = 7.4, 7.4 Hz), 7.32 (2H, dd, J = 7.4, 7.4 Hz), 6.46 (1H, dd, J = 2.3, 2.3 Hz), 6.43 (2H, d, J = 2.3 Hz), 5.24 (1H, t, J = 7.9 Hz), 5.02 (4H, s), 3.69 (6H, s), 3.56 (1H, t, J = 7.9 Hz), 2.58 (2H, d, J = 7.9 Hz), 2.54 (2H, t, J = 7.9 Hz), 2.26 (2H, dt, J = 7.9 Hz), 1.59 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 159.9, 144.4, 136.9, 131.5, 128.5, 127.9, 127.5, 126.6, 107.6, 99.4, 70.0, 52.4, 50.6, 38.5, 36.1, 29.6, 15.7; IR (neat) ν_{max} 3031, 2951, 2248, 1732, 1592, 1947, 1451, 1435, 1343, 1288, 1234, 1147, 1054, 1027, 907, 829, 727, 695, 647 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{31}H_{34}NaO_6$: 525.2248, found: 525.2250.

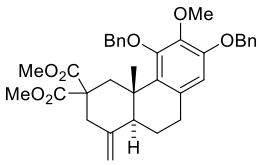
dimethyl
(*E*)-2-(5-(3,5-bis(benzyloxy)phenyl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (48)



To a stirred suspension of sodium hydride (36.4 mg, 0.911 mmol, 1.3 equiv) in THF (5 mL) was added **61a** (352 mg, 0.701 mmol) in THF (1 mL×3) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. Then, to a stirred solution, propargyl bromide (0.079 mL, 1.05 mmol, 1.5 equiv) was added, and stirred for 4 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **48** (364 mg, 96%) as colorless oil:
R_f = 0.31 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (4H, d, J = 7.4 Hz), 7.38 (4H, dd, J = 7.4, 7.4 Hz), 7.32 (2H, dd, J = 7..4, 7.4 Hz), 6.46 (1H, dd, J = 2.3, 2.3 Hz), 6.45 (2H, d, J = 2.3 Hz), 5.36 (1H, t, J = 7.4 Hz), 5.02 (4H, s), 3.71 (6H, s), 2.79 (2H, s), 2.75 (2H, d, J = 2.3 Hz), 2.58 (2H, t, J = 7.4 Hz), 2.29 (2H, dt, J = 7.4, 7.4 Hz), 2.01 (1H, t, J = 2.3 Hz), 1.50 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.9, 144.4, 138.0, 130.2, 129.8, 128.5, 127.9, 127.5, 107.7, 99.5, 79.4, 71.6, 70.0, 56.7, 52.6, 41.5, 35.9, 29.7, 22.5, 16.8; IR (neat) ν_{max} 3288, 3064, 3031, 2951, 2860, 1736, 1592, 1452, 1375, 1289, 1210, 1154, 1099, 1058, 829, 736, 696, 645 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{34}H_{36}NaO_6$: 563.2404, found: 563.2405.

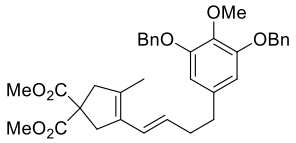
dimethyl

(4a*S,10a*S**)-5,7-bis(benzyloxy)-6-methoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydro phenanthrene-3,3(2*H*)-dicarboxylate (62c)**



dimethyl

(*E*)-3-(4-(3,5-bis(benzyloxy)-4-methoxyphenyl)but-1-en-1-yl)-4-methylcyclopent-3-ene-1,1-dica rboxylate (62c')

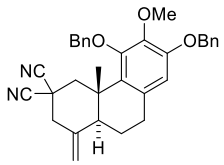


According to general procedure, **62c** was obtained as colorless oil (65%) and **62c'** was obtained as colorless oil (31%):

62c: R_f = 0.76 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 7.4 Hz), 7.46 (2H, d, *J* = 7.4 Hz), 7.40 (4H, dd, *J* = 7.4, 7.4 Hz), 7.33 (2H, dd, *J* = 7.4, 7.4 Hz), 6.49 (1H, s), 5.21 (1H, d, *J* = 11.3 Hz), 5.14 (1H, br), 5.13 (1H, d, *J* = 11.3 Hz), 5.09 (2H, s), 4.77 (1H, br), 3.95 (1H, d, *J* = 14.2 Hz), 3.83 (3H, s), 3.68 (3H, s), 3.39 (3H, s), 3.20 (1H, d, *J* = 13.0 Hz), 2.99-2.57 (2H, m), 2.27 (1H, d, *J* = 13.0 Hz), 2.20 (1H, d, *J* = 12.5 Hz), 2.16 (1H, d, *J* = 14.2 Hz), 1.81-1.52 (2H, m), 1.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 172.4, 152.3, 150.9, 145.1, 141.4, 138.2, 137.1, 132.3, 131.7, 128.5, 128.2, 128.1, 128.1, 127.8, 127.5, 127.5, 127.3, 110.8, 109.7, 74.7, 70.7, 65.8, 60.9, 55.0, 52.8, 51.8, 50.0, 40.7, 40.6, 39.7, 31.6, 20.9, 19.1, 15.3; IR (neat) ν_{max} 2949, 2251, 1730, 1593, 1485, 1433, 1338, 1255, 1240, 1205, 1092, 1026, 965, 905, 849, 726, 647, 546 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{38}NaO_7$: 593.2510, found: 593.2509.

62': R_f = 0.66 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (4H, d, *J* = 7.4 Hz), 7.37 (4H, dd, *J* = 7.4, 7.4 Hz), 7.31 (2H, dd, *J* = 7.4, 7.4 Hz), 6.46 (2H, s), 6.23 (1H, d, *J* = 14.7 Hz), 5.53 (1H, dt, *J* = 14.7, 7.4 Hz), 5.11 (4H, s), 3.88 (3H, s), 3.72 (6H, s), 3.10 (2H, s), 3.04 (2H, s), 2.58 (2H, t, *J* = 7.4 Hz), 2.35 (2H, dt, *J* = 7.4, 7.4 Hz), 1.73 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 152.4, 137.4, 132.2, 130.6, 130.0, 128.5, 127.8, 127.3, 124.2, 108.2, 71.2, 65.8, 60.9, 57.0, 52.8, 46.4, 41.2, 36.2, 34.9, 15.3, 13.4; IR (neat) ν_{max} 3031, 2927, 2853, 1734, 1588, 1506, 1434, 1372, 1327, 1254, 1198, 1164, 1113, 1075, 1009, 965, 821, 737, 698 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{38}NaO_7$: 593.2510, found: 593.2509.

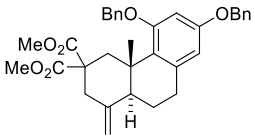
(4aS,10a*S)-5,7-bis(benzyloxy)-6-methoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2H)-dicarbonitrile (62d)**



According to *general procedure*, **62d** was obtained as colorless oil (quantitative yield). Ee was determinded by HPLC (220 nm); Daicel CHIRALPAK® IC-3 0.46 cm φ × 25 cm; hexane/2-propanol = 24/1; flow rate 1.0 mL/min; retention time: 27.0 min for **62d**, 38.4 min for ***ent*-62d**:

R_f = 0.32 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.4 Hz), 7.45 (4H, dd, *J* = 7.4, 7.4 Hz), 7.42-7.29 (4H, m), 6.48 (1H, s), 5.28 (1H, d, *J* = 10.8 Hz), 5.25 (1H, br), 5.13-5.06 (3H, m), 4.97 (1H, br), 3.97 (1H, dd, *J* = 15.3, 2.3 Hz), 3.86 (3H, s), 3.00 (1H, dd, *J* = 13.0, 2.3 Hz), 2.93-2.83 (1H, m), 2.81 (1H, ddd, *J* = 15.3, 15.3, 4.0 Hz), 2.67 (1H, d, *J* = 13.0 Hz), 2.16 (1H, d, *J* = 13.0 Hz), 1.96 (1H, d, *J* = 15.3 Hz), 1.84-1.76 (1H, m), 1.72 (1H, dddd, *J* = 13.0, 13.0, 13.0, 4.0 Hz), 1.37 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 151.4, 141.2, 140.8, 137.2, 136.9, 131.0, 130.1, 128.8, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7, 127.3, 116.7, 116.2, 114.5, 109.7, 75.5, 70.7, 60.9, 49.3, 44.1, 43.3, 40.0, 32.0, 31.0, 20.9, 20.2; IR (neat) ν_{max} 3032, 2936, 2879, 2248, 1593, 1570, 1486, 1435, 1414, 1340, 1259, 1143, 1095, 1025, 907, 848, 730, 696, 647 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{33}H_{32}N_2NaO_3$: 527.2305, found: 527.2308.

dimethyl
(4a*S,10a*S**)-5,7-bis(benzyloxy)-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2H)-dicarboxylate (63)**



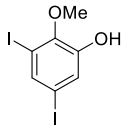
According to *general procedure*, **63** was obtained as colorless oil (99%):

R_f = 0.34 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.30 (10H, m), 6..49 (1H, d, *J* = 2.3 Hz), 6.34 (1H, d, *J* = 2.3 Hz), 5.12 (1H, br), 5.04 (1H, d, *J* = 11.3 Hz), 5.01 (2H, s), 4.96 (1H, d, *J* = 11.3 Hz), 4.75 (1H, br), 4.01 (1H, dd, *J* = 13.6, 1.7 Hz), 3.68 (3H, s), 3.29 (3H, s), 3.18 (1H, dd, *J* = 13.6, 1.7 Hz), 2.93 (1H, ddd, *J* = 17.0, 12.5, 5.1 Hz), 2.80 (1H, dd, *J* = 17.0, 5.1 Hz), 2.27 (1H, d, *J* = 13.6 Hz), 2.21 (1H, d, *J* = 12.5 Hz), 2.01 (1H, d, *J* = 13.6 Hz), 1.80-1.72 (1H, m), 1.68 (1H, ddd, *J* = 12.5, 12.5, 5.1 Hz), 0.97 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 172.4, 158.9, 157.4, 145.3, 138.3, 137.1, 136.8, 128.6, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 127.6, 127.2, 120.9, 110.5, 106.3, 99.0, 70.7, 70.0, 54.9, 52.7, 51.7, 50.5, 40.7, 40.0, 39.3, 32.1, 20.7,

17.6; IR (neat) ν_{max} 3032, 2948, 2873, 2841, 1730, 1600, 1578, 1453, 1431, 1262, 1239, 1205, 1153, 1072, 1045, 906, 730, 697 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{34}H_{36}NaO_6$: 563.2404, found: 563.2405.

第3章　第3節

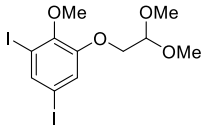
3,5-diiodo-2-methoxyphenol (66)



To a stirred solution of 2,4,6-triiodoanisole **65** (77.2g, 159 mmol) in Et_2O (1.6 L) was added *n*BuLi (1.54M in *n*-hexane, 103 mL, 159 mmol, 1.0 equiv) at –78 °C and the reaction mixture was stirred for 30 min at –78 °C. Then, to the stirred solution, trimethylborate (17.6 mL, 159 mmol, 1.0equiv) was added, and stirred for 30 min at –78 C. Then, to the stirred solution sodium perborate tetrahydrate (244 g, 1590 mmol, 10 equiv) was added and warmed to rt. After stirring for 16 h, to the reaction mixture was added saturated aqueous NH_4Cl solution (500 mL). The aqueous layer was extracted with Et_2O (200 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated to afford the product **66** (59.2 g, 99%) as white solid, which was used without further purification:

R_f = 0.38 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 1.8 Hz), 7.27 (1H, d, *J* = 1.8 Hz), 5.60 (1H, br), 3.84 (3H, s).

1-(2,2-dimethoxyethoxy)-3,5-diiodo-2-methoxybenzene (66a)

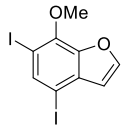


To a stirred solution of **66** (59.2g, 157 mmol), K_2CO_3 (26.1 g, 189 mmol, 1.2 equiv) and TBAI (5.82 g, 15.7 mmol, 0.1 equiv) in DMF (230 mL) was bromoacetaldehyde dimethylacetal (**67**) (22.2 mL, 189 mmol, 1.2 equiv) at room temperature and the reaction mixture was stirred for 4 h at 100 °C. After disappearance of the starting material, the reaction mixture was filtered through Celite® pad and wash with Et_2O (100 mL×3). The filtrated was concentrated and added Et_2O (200 mL) and H_2O 200 mL). Then, the aqueous layer was extracted with Et_2O (200 mL×3), and the combined organic layer was washed with H_2O (200 mL×2), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **66a** (75.4 g, 86%) as colorless oil:

R_f = 0.55 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 1.8 Hz), 7.16

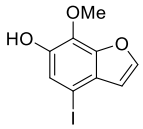
(1H, d, J = 1.8 Hz), 4.73 (1H, t, J = 5.5 Hz), 3.99 (2H, d, J = 5.5 Hz), 3.83 (3H, s), 3.46 (6H, s).

4,6-diiodo-7-methoxybenzofuran (68)



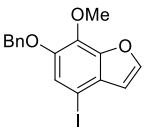
To polyphosphoric acid (38.6 g, 100 wt %) was added a stirred solution of **66a** (38.6 g, 83.2 mmol) in toluene (800 mL) at room temperature and the reaction mixture was stirred for 2 h at 100 °C. After disappearance of the starting material, the reaction mixture was added saturated aqueous $NaHCO_3$.solution (400 mL) The aqueous layer was extracted with Et_2O (200 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **68** (26.3 g, 79%) as white solid:
R_f = 0.75 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, s), 7.59 (1H, d, J = 3.7 Hz), 6.67 (1H, d, J = 3.7 Hz), 4.21 (3H, s).

4-iodo-7-methoxybenzofuran-6-ol (68a)



To a stirred solution of **68** (24.2 g, 61.0 mmol) in Et_2O (300 mL) was added *n*BuLi (1.54M in *n*-hexane, 39.6 mL, 61.0 mmol, 1.0 equiv) at –78 °C and the reaction mixture was stirred for 30 min at –78 °C. Then, to the stirred solution, trimethylborate (6.74 mL, 61.0 mmol, 1.0 equiv) was added, and stirred for 2 h at 0 °C. Then, to the stirred solution sodium perborate tetrahydrate (46.9 g, 305 mmol, 5.0 equiv) was added and warmed to rt. After stirring for 16 h, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (100 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **68a** (15.9 g, 90%) as white solid:
R_f = 0.34 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 1.8 Hz), 7.29 (1H, s), 6.59 (1H, d, J = 1.8 Hz), 5.56 (1H, s), 4.21 (3H, s).

6-(benzyloxy)-4-iodo-7-methoxybenzofuran (69)

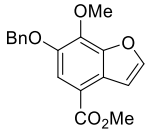


To a stirred solution of **68a** (11.9 g, 41.3 mmol) and K_2CO_3 (6.86 g, 49.6 mmol, 1.2equiv) in

acetone (150 mL) was benzyl bromide (6.0 mL, 45.4 mmol, 1.1 equiv) at room temperature and the reaction mixture was stirred for 4 h at reflux temperature. After disappearance of the starting material, the reaction mixture was filtered through Celite® pad and wash with Et_2O (50 mL×3). The filtrated was concentrated and dilute with EtOAc (100 mL) and H_2O (100 mL). Then, the aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **69** as white solid quantitatively:

R_f = 0.68 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 1.8 Hz), 7.46 (2H, d, *J* = 7.3 Hz), 7.39 (2H, dd, *J* = 7.3, 7.3 Hz), 7.33 (1H, dd, *J* = 7.3, 7.3 Hz), 7.31 (1H, s), 6.58 (1H, d, *J* = 1.8 Hz), 5.14 (2H, s), 4.13 (3H, s).

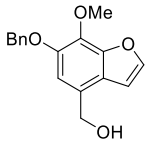
methyl 6-(benzyloxy)-7-methoxybenzofuran-4-carboxylate (70)



To a stirred solution of **69** (16.0 g, 42.1 mmol) and $Pd(PPh_3)_4$ (4.87 g, 4.21 mmol, 0.1 equiv) in MeOH (50 mL) was Et_3N (17.6 mL, 126 mmol, 3.0 equiv) at room temperature and filled with CO gas. The mixture was stirred for 12 h at 50 °C under CO atmosphere (1 atm). After disappearance of the starting material, the reaction vessel was filled with argon. Then, to the solution was added NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (100 mL×3), and the combined organic layer was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **70** (12.3 g, 94%) as white solid.

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, s), 7.66 (1H, d, *J* = 2.3 Hz), 7.49 (2H, d, *J* = 7.3 Hz), 7.39 (2H, dd, *J* = 7.3, 7.3 Hz), 7.32 (1H, dd, *J* = 7.3, 7.3 Hz), 7.29 (1H, d, *J* = 2.3 Hz), 5.19 (2H, s), 4.27 (3H, s), 3.95 (3H, s).

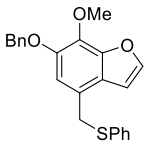
(6-(benzyloxy)-7-methoxybenzofuran-4-yl)methanol (70a)



To a stirred solution of $LiAlH_4$ (1.41 g, 29.7 mmol, 0.75 equiv) in THF (200 mL) was added **70** (12.3 g, 39.6 mmol) in THF (20 mL×3) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 solution, filtered through a plug of Celite®, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 2/1) to afford the product **70a** as white amorphous quantatively:

R_f = 0.10 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 2.3 Hz), 7.47 (2H, d, *J* = 7.3 Hz), 7.38 (2H, dd, *J* = 7.3, 7.3 Hz), 7.32 (1H, dd, *J* = 7.3, 7.3 Hz), 6.98 (1H, s), 6.84 (1H, d, *J* = 2.3 Hz), 5.18 (2H, s), 4.81 (2H, s), 4.14 (3H, s).

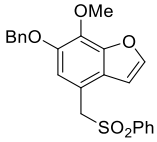
6-(benzyloxy)-7-methoxy-4-((phenylthio)methyl)benzofuran (70b)



To a solution of **70a** (11.0 g, 38.8 mmol) and diphenyl disulfide (12.7 g, 58.2 mmol, 1.5 equiv) in THF (200 mL) was added tributylphosphine (16.1 mL, 58.2 mmol, 1.5 equiv), and the reaction mixture was stirred for 2 h at room temperature. After disappearance of the starting material, to the reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **70b** (14.5 g, 99%).

R_f = 0.53 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz), 7.44-7.17 (10H, m), 6.80 (1H, s), 6.75 (1H, d, *J* = 2.3 Hz), 5.05 (2H, s), 4.22 (2H, s), 4.11 (3H, s).

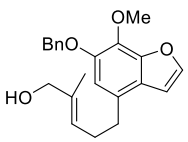
6-(benzyloxy)-7-methoxy-4-((phenylsulfonyl)methyl)benzofuran (71)



To a stirred solution of **70b** (14.2 g, 37.9 mmol) in THF/MeOH/H_2O (150 mL/150 mL/150 mL, 1/1/1) was added Oxone® (35.0 g, 114 mmol, 3.0 equiv) at 0 °C and the reaction mixture was stirred for 4 h at room temperarture. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous Na_2SO_3 solution (200 mL). The aqueous layer was extracted with EtOAc (100 mL×3), dried over Na_2SO_4, and evaporated to form white solid. The residue was collected and washed with hexane (100 mL×3) to afford the product **71** (14.9 g, 96%) as white solid, which was used a next step without further purification:

R_f = 0.41 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.7 Hz), 7.47 (1H, d, *J* = 2.3 Hz), 7.43-7.28 (8H, m), 6.63 (1H, s), 6.46 (1H, d, *J* = 2.3 Hz), 4.98 (2H, s), 4.43 (2H, s), 4.14 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{23}H_{20}NaO_5S$: 431.1, found: 431.1.

(*E*)-5-(6-(benzyloxy)-7-methoxybenzofuran-4-yl)-2-methylpent-2-en-1-ol (72)



To a stirred solution of **71** (1.52 g, 3.72 mmol), TBAI (0.138 g, 0.373, 0.1 equiv), DMPU (4.5 mL,

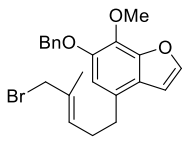
37.2 mmol, 10 euqiv) in THF (30 mL) was added *n*BuLi (1.61M in *n*-hexane, 2.4 mL, 3.91 mmol, 1.05 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at 0 °C. Then, a stirred solution was cooled to –78 °C again, **51** (1.15g, 4.10 mmol, 1.1 equiv) in THF (3 mL×3) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

To a solution of crude material in MeOH (30 mL) was added magnesium turnings (903 mg, 37.2mmol, 10 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C and warm to rt. After 4 h stirring, to the mixture was added saturated 1M HCl solution (10 mL) and stirred until consumption of magnesium. The aqueous layer was extracted with EtOAc (20 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification.

To a stirred solution of crude material in THF (30 mL) was added tetrabutylammonium fluoride (1.0M in THF, 7.4 mL, 7.44 mmol, 2.0 equiv), and the reaction mixture was stirred for 1 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford the product **72** (787 mg, 60% over 3 steps) as pale-yellow oil:

R_f = 0.60 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3. Hz), 7.47 (2H, d, *J* = 7.3 Hz), 7.38 (2H, dd, *J* = 7.3, 7.3 Hz), 7.31 (1H, dd, *J* = 7.3, 7.3 Hz), 6.76 (1H, s), 6.71 (1H, d, *J* = 2.3 Hz), 5.44 (1H, t, *J* = 7.8 Hz), 5.17 (2H, s), 4.11 (3H, s), 3.96 (2H, s), 2.78 (2H, t, *J* = 7.8 Hz), 2.36 (2H, dt, *J* = 7.8, 7.8 Hz), 1.57 (3H, s), 1.49 (1H, br).

6-(benzyloxy)-4-((*E*)-5-bromo-4-methylpent-3-enyl)-7-methoxybenzofuran (73)

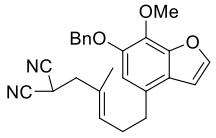


To a stirred solution of **72** (523 mg, 1.48 mmol) and triphenylphosphine (468 mg, 1.78 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) was added carbon tetrabromide (591 mg, 1.78 mmol, 1.3 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **73** (588 mg, 95%) as colorless oil:

R_f = 0.57 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 2.3 Hz), 7.47

(2H, d, *J* = 7.3 Hz), 7.38 (2H, dd, *J* = 7.3, 7.3 Hz), 7.32 (1H, dd, *J* = 7.3, 7.3 Hz), 6.74 (1H, s), 6.70 (1H, d, *J* = 2.3 Hz), 5.60 (1H, t, *J* = 7.8 Hz), 5.17 (2H, s), 4.12 (3H, s), 3.92 (2H, s), 2.78 (2H, t, *J* = 7.8 Hz), 2.35 (2H, dt, *J* = 7.8, 7.8 Hz), 1.67 (3H, s).

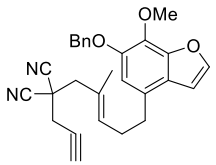
(*E*)-2-(5-(6-(benzyloxy)-7-methoxybenzofuran-4-yl)-2-methylpent-2-en-1-yl)malononitrile (73a)



To a stirred solution of **73** (421 mg, 1.01 mmol), malononitrile (100 mg, 1.52 mmol, 1.5 equiv) and tetrabtuylammonium iodide (37.4 mg, 0.101 mmol, 0.1 equiv) in CH_2Cl_2 (10 mL) was added *i*Pr_2NEt (0.17 mL, 1.01 mmol, 1.0 equiv) and the reaction mixture was stirred for 24 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), dried over Na_2SO_4, and evaporated. The residue was roughly purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **73a** as pale-yellow oil, which was pure enough for the next reaction:

R_f = 0.55 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 2.3 Hz), 7.47 (2H, d, *J* = 7.3 Hz), 7.38 (2H, dd, *J* = 7.3, 7.3 Hz), 7.32 (1H, dd, *J* = 7.3, 7.3 Hz), 6.75 (1H, s), 6.71 (1H, d, *J* = 2.3 Hz), 5.48 (1H, t, *J* = 7.3 Hz), 5.18 (2H, s), 4.12 (3H, s), 3.71 (1H, t, *J* = 7.3 Hz), 2.79 (2H, t, *J* = 7.3 Hz), 2.60 (2H, d, *J* = 7.3 Hz), 2.39 (2H, dt, *J* = 7.3, 7.3 Hz), 1.58 (3H, s).

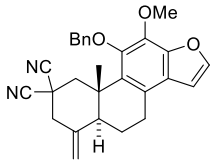
(*E*)-2-(5-(6-(benzyloxy)-7-methoxybenzofuran-4-yl)-2-methylpent-2-en-1-yl)-2-(prop-2-yn-1-yl)malononitrile (64)



To a stirred solution of crude **73a** in THF (10 mL) was added *n*BuLi (1.61M in *n*-hexane, 0.98 mL, 1.51 mmol, 1.5 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution, propargyl bromide (0.11 mL, 1.51 mmol, 1.5 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (5 mL×3), and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **74** (429 mg, 97% over 2 steps) as beige solid:

R_f = 0.28 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 2.3 Hz), 7.47 (2H, d, *J* = 7.3 Hz), 7.38 (2H, dd, *J* = 7.3, 7.3 Hz), 7.32 (1H, dd, *J* = 7.3, 7.3 Hz), 6.77 (1H, s), 6.72 (1H, d, *J* = 2.3 Hz), 5.55 (1H, t, *J* = 7.3 Hz), 5.17 (2H, s), 4.11 (3H, s), 2.82 (2H, t, *J* = 7.3 Hz), 2.80 (2H, d, *J* = 2.8 Hz), 2.67 (2H, s), 2.42 (2H, dt, *J* = 7.3, 7.3 Hz), 2.38 (1H, t, *J* = 2.8 Hz), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 147.2, 144.4, 137.4, 134.2, 133.5, 128.5, 127.8, 127.8, 127.5, 127.4, 122.9, 114.7, 112.9, 105.1, 75.4, 74.7, 72.8, 61.1, 45.5, 36.2, 32.3, 29.2, 28.2, 17.1; IR (neat) ν_{max} 3290, 2932, 1654, 1618, 1542, 1504, 1454, 1438, 1398, 1315, 1224, 1122, 1042, 738, 698 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{26}N_2NaO_3$: 461.1836, found: 461.1836.

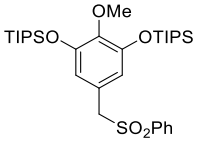
(5a*S,9a*S**)-10-(benzyloxy)-5,5a,6,7,9,9a-hexahydro-11-methoxy-9a-methyl-6-methylenephenanthro[2,1-b]furan-8,8(4*H*)-dicarbonitrile (74)**



According to *general procedure*, **11** was obtained as colorless oil (75%). Ee was determinded by HPLC (254 nm); Daicel CHIRALPAK® IC-3 0.46 cm φ × 25 cm; hexane/2-propanol = 24/1; flow rate 1.0 mL/min; retention time: 25.9 min for **74**, 41.6 min for ***ent*-74**:

R_f = 0.39 (hexane/ethyl acetate = 4/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 2.3 Hz), 7.55 (2H, d, *J* = 7.3 Hz), 7.47 (2H, dd, *J* = 7.3, 7.3 Hz), 7.39 (1H, dd, *J* = 7.3, 7.3 Hz), 6.72 (1H, d, *J* = 2.3 Hz), 5.29 (1H, d, *J* = 10.5 Hz), 5.29 (1H, s), 5.08 (1H, d, *J* = 10.5 Hz), 5.02 (1H, s), 4.15 (3H, s), 4.14-4.06 (1H, m), 3.08-2.89 (3H, m), 2.69 (1H, d, *J* = 13.3 Hz), 2.25 (1H, d, *J* = 12.4 Hz), 2.01-1.74 (3H, m), 1.44 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 147.5, 145.7, 144.9, 141.1, 137.4, 133.0, 129.1, 128.7, 128.3, 124.4, 122.2, 116.9, 116.5, 114.9, 105.6, 76.0, 61.1, 49.8, 44.4, 43.5, 40.8, 32.3, 30.5, 27.9, 20.7, 20.3; IR (neat) ν_{max} 2944, 2882, 2359, 2339, 1654, 1471, 1330, 1143, 1120, 1049, 1030, 989, 975, 913, 751 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{26}N_2NaO_3$: 461.1836, found: 461.1837.

((2-methoxy-5-((phenylsulfonyl)methyl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (76)

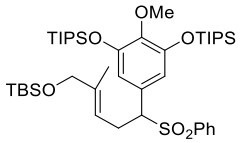


According to modified Murakami's procedure[49], to a stirred solution of **75**[50] (50. 2g, 104 mmol) in DMF (400 mL) was added Et_3N (18.8 mL, 135 mmol, 1.3 equiv), then MsCl (9.7 mL, 124 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added sodium benzenesulfinate (25.6 g, 156 mmol,

1.5equiv) and potassium iodide (25.9 g, 156 mmol, 1.5 equiv). After stirring for 4 h at 70 °C, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (150 mL×5), and the combined organic layer was washed with H_2O (100 mL×3), brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1 to 30/1) to afford the product **76** (61.5 g, 97%) as colorless solid:

R_f = 0.30 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 7.3 Hz), 7.56 (1H, dd, *J* = 7.3, 7.3 Hz), 7.41 (2H, dd, *J* = 7.3, 7.3 Hz), 6.23 (2H, s), 4.16 (2H, s), 3.73 (3H, s), 1.16 (6H, qq, *J* = 7.8, 7.8 Hz), 1.04 (36H, d, *J* = 7.8 Hz).

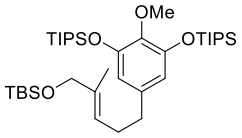
(*E*)-((2-methoxy-5-(4-methyl-1-(phenylsulfonyl)-5-((triisopropylsilyl)oxy)pent-3-en-1-yl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (76a)



To a stirred solution of **76** (21.9 g, 36.1 mmol), TBAI (1.33 g, 3.61 mmol, 0.1 equiv), DMPU (21.9 ml, 180 mmol, 5.0 equiv) in THF (150 mL) was added *n*BuLi (1.64M in *n*-hexane, 26.4 mL, 43.4 mmol, 1.1 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at 0 °C. Then, a stirred solution was cooled to –78 °C again, **51** (13.1 g, 47.0 mmol, 1.2 equiv) in THF (10 mL×3) was added. The reaction mixture was warmed to room temperature and stirred for 16 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (150 mL×3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **76a** (22.2 g, 76%) as pale-yellow oil:

R_f = 0.43 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 7.3 Hz), 7.50 (1H, dd, *J* = 7.3 Hz), 7.35 (2H, dd, *J* = 7.3 Hz), 6.27 (2H, s), 5.08 (1H, t, *J* = 6.8 Hz), 3.87 (2H, br), 3.84 (1H, dd, *J* = 14.2, 3.2 Hz), 3.71 (3H, s), 3.23 (1H, ddd, *J* = 14.2, 6.8, 3.2 Hz), 2.73 (1H, ddd, *J* = 14.2, 14.2, 6.8 Hz), 1.59 (3H, s), 1.16 (6H, qq, *J* = 6.9, 6.9 Hz), 1.04 (36H, d, *J* = 6.9 Hz), 0.81 (9H, s), 0.07 (6H, s).

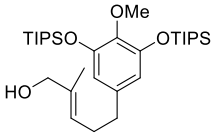
(*E*)-((5-(5-((tert-butyldimethylsilyl)oxy)-4-methylpent-3-en-1-yl)-2-methoxy-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (76b)



To a solution of **76a** (17.2 g, 21.4 mmol) in MeOH (200 mL) was added magnesium turnings (5.20 g, 214 mmol, 10 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C and warm to rt. After 4 h stirring, to the mixture was added saturated 1M HCl solution (200 mL) and stirred until consumption of magnesium. The aqueous layer was extracted with EtOAc (150 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **76b** (13.9 g, 92%) as pale-yellow oil:

R_f = 0.83 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (2H, s), 5.39 (1H, t, *J* = 7.8 Hz), 3.98 (2H, s), 3.74 (3H, s), 2.47 (2H, t, *J* = 7.8 Hz), 2.25 (2H, dt, *J* = 7.8, 7.8 Hz), 1.57 (3H, s), 1.25 (6H, qq, *J* = 7.3, 7.3 Hz), 1.10 (36H, d, *J* = 7.3 Hz), 0.90 (9H, s), 0.05 (6H, s).

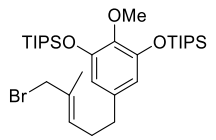
(*E*)-5-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)-2-methylpent-2-en-1-ol (77)



To a stirred solution of **76b** (3.73 g, 5.61 mmol) in THF/H_2O (45 mL/5 mL, 9/1) was added PTSA·H_2O (2.13 g, 11.2 mmol, 2.0 equiv), and the reaction mixture was stirred for 1 h at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with EtOAc (150 mL×3), and the combined organic layer was washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **77** (2.72 g, 88%) as pale-yellow oil:

R_f = 0.38 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (2H, s), 5.41 (1H, t, *J* = 7.8 Hz), 3.96 (2H, s), 3.74 (3H, s), 2.49 (2H, t, *J* = 7.8 Hz), 2.27 (2H, dt, *J* = 7.8, 7.8 Hz), 1.63 (3H, s), 1.26 (6H, qq, *J* = 7.3, 7.3 Hz), 1.10 (36H, d, *J* = 7.3 Hz).

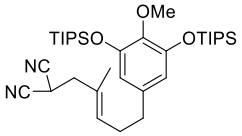
(*E*)-((5-(5-bromo-4-methylpent-3-en-1-yl)-2-methoxy-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (77a)



To a stirred solution of **77** (8.39 g, 15.2 mmol) and triphenylphosphine (5.59 g, 22.8 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added carbon tetrabromide (5.99 g, 22.8 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, reaction mixture was evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford the product **77a** (9.05 g, 97%) as colorless oil:

R_f = 0.95 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (2H, s), 5.58 (1H, t, *J* = 7.3 Hz), 3.93 (2H, s), 3.74 (3H, s), 2.49 (2H, t, *J* = 7.3 Hz), 2.27 (2H, dt, *J* = 7.3, 7.3 Hz), 1.72 (3H, s), 1.25 (6H, qq, *J* = 7.3, 7.3 Hz), 1.10 (36H, d, *J* = 7.3 Hz).

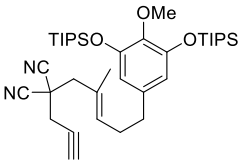
(*E*)-2-(5-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)-2-methylpent-2-en-1-yl)malononitril e (77b)



To a stirred suspension of NaH (362 mg, 9.06 mmol, 1.0 equiv) in THF (100 mL) was added malononitrile (897 mg, 13.6 mmol, 1.5 equiv) in THF (20 mL) and the reaction mixture was stirred for 30 min at 0 °C. After stirring, **77a** (5.56 g, 9.06 mmol) was added. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with Et_2O (50 mL×3), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford the product **77b** (3.87 g, 71%) as pale-yellow oil:

R_f = 0.43 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (2H, s), 5.49 (1H, t, *J* = 7.3 Hz), 3.75 (1H, t, *J* = 7.8 Hz), 3.74 (3H, s), 2.64 (2H, d, *J* = 7.8 Hz), 2.49 (2H, t, *J* = 7.3 Hz), 2.29 (2H, dt, *J* = 7.3, 7.3 Hz), 1.67 (3H, s), 1.26 (6H, qq, *J* = 7.3, 7.3 Hz), 1.10 (36H, d, *J* = 7.3 Hz).

(*E*)-2-(5-(4-methoxy-3,5-bis((triisopropylsilyl)oxy)phenyl)-2-methylpent-2-en-1-yl)-2-(prop-2-y n-1-yl)malononitrile (78)

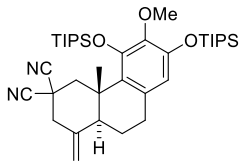


To a stirred solution of **77b** (5.16 g, 8.61 mmol) in THF (50 mL) was added *n*BuLi (1.64M in *n*-hexane, 5.3 mL, 8.61 mmol, 1.0 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution, propargyl bromide (0.65 mL, 8.61 mmol, 1.0 equiv) in THF (20 mL) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (50 mL×3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford the product **78** (4.88 g, 89%) as colorless oil:

R_f = 0.48 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (2H, s), 5.56 (1H, t, *J* =

7.3 Hz), 3.74 (3H, s), 2.86 (2H, d, *J* = 2.8 Hz), 2.70 (2H, s), 2.52 (2H, t, *J* = 7.3 Hz), 2.39 (1H, t, *J* = 2.8 Hz), 2.32 (2H, dt, *J* = 7.3, 7.3 Hz), 1.81 (3H, s), 1.26 (6H, qq, *J* = 7.3, 7.3 Hz), 1.10 (36H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 140.6, 136.2, 134.0, 127.0, 114.7, 113.6, 75.4, 74.7, 60.3, 45.7, 36.5, 34.9, 30.1, 28.3, 17.9, 17.1, 12.8; IR (neat) ν_{max} 3310, 2943, 2892, 2866, 2360, 2340, 1575, 1494, 1429, 1356, 1226, 1097, 1068, 1013, 910, 882, 834, 682 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{37}H_{60}N_2NaO_3Si_2$: 659.4035, found: 659.4031.

(4a*S,10a*S**)-6-methoxy-4a-methyl-1-methylene-5,7-bis((triisopropylsilyl)oxy)-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2*H*)-dicarbonitrile (79)**

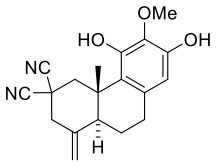


According to *general procedure*, **79** was obtained as colorless oil (94%, 86% ee). Ee was determinded by HPLC (220 nm); Daicel CHIRALPAK® IC-3 0.46 cm φ × 25 cm; hexane/2-propanol = 400/1; flow rate 1.0 mL/min; retention time: 20.7 min for ***ent*-79**, 38.4 min for **79**:

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, s), 5.27 (1H, br), 4.98 (1H, br), 4.28 (1H, dd, *J* = 14.2, 1.8 Hz), 3.78 (3H, s), 3.04 (1H, dd, *J* = 13.3, 1.8 Hz), 2.89-2.78 (1H, m), 2.77-2.66 (1H, m), 2.70 (1H, d, *J* = 13.3 Hz), 2.15 (1H, dd, *J* = 9.2, 5.0 Hz), 1.97 (1H, d, *J* = 14.2 Hz), 1.79-1.67 (2H, m), 1.45 (3H, qq, *J* = 7.3, 7.3 Hz), 1.42 (3H, s), 1.24 (3H, qq, *J* = 7.3, 7.3 Hz), 1.19-1.05 (36H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.7, 141.0, 139.6, 129.7, 127.6, 116.8, 116.3, 114.4, 113.4, 60.2, 49.7, 44.3, 42.2, 39.9, 32.1, 30.8, 20.7, 19.3, 18.4, 18.4, 17.8, 14.3, 12.9; IR (neat) ν_{max} 2946, 2892, 2867, 2359, 2341, 1436, 1411, 1352, 1255, 1142, 1099, 1017, 881, 809, 758, 680, 655 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{37}H_{60}N_2NaO_3Si_2$: 659.4035, found: 659.4034.

第4章

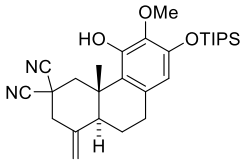
(4a*S,10a*S**)-5,7-dihydroxy-6-methoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2*H*)-dicarbonitrile (85)**



To a stirred solution of **62d** (506 mg, 1.00 mmol) and anisole (1.1 mL, 10.0 mmol, 10 equiv) in

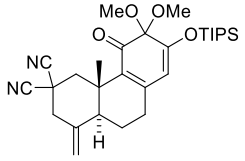
CH_2Cl_2 (10 mL) was added boron trichloride (1.0M in CH_2Cl_2, 2.5 mL, 2.5 mmol, 2.5 equiv) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added MeOH and evapolated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford the product **85** as white solid quantitatively:
R_f = 0.35 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (1H, s), 5.74 (1H, s), 4.92 (1H, br), 4.83 (1H, s), 4.55 (1H, s), 3.84 (3H, s), 3.11 (1H, ddd, *J* = 12.4, 3.2, 3.2 Hz), 2.82 (1H, ddd, *J* = 16.9, 12.4, 6.4 Hz), 2.72 (1H, ddd, *J* = 16.9, 6.4, 3.2 Hz), 2.56 (1H, ddd, *J* = 12.4, 3.2, 3.2 Hz), 2.16 (1H, d, *J* = 12.4 Hz), 1.81-1.59 (3H, m), 1.45-1.34 (1H, m), 1.12 (3H, s).

(4a*S,10a*S**)-5-hydroxy-6-methoxy-4a-methyl-1-methylene-7-((triisopropylsilyl)oxy)-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2*H*)-dicarbonitrile (85a)**



To a solution of **85** (306 mg, 0.943 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.22 mL, 1.89 mmol, 2.0 equiv), then TIPSOTf (0.38 mL, 1.41 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **85a** (396 mg, 87%) as colorless oil:
R_f = 0.85 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, s), 6.15 (1H, s), 5.27 (1H, s), 4.97 (1H, s), 4.08 (1H, d, *J* = 14.2 Hz), 3.87 (3H, s), 3.05 (1H, dd, *J* = 13.2, 2.3 Hz), 2.82 (1H, ddd, *J* = 17.8, 10.5, 6.9 Hz), 2.76-2.66 (2H, m), 2.21 (1H, d, *J* = 10.5 Hz), 2.04 (1H, d, *J* = 14.2 Hz), 1.84-1.66 (2H, m), 1.39 (3H, s), 1.28 (3H, qq, *J* = 7.8, 7.8 Hz), 1.15-1.06 (18H, m).

(4a*S,10a*S**)-6,6-dimethoxy-4a-methyl-1-methylene-5-oxo-7-((triisopropylsilyl)oxy)-1,4,4a,5,6,9,10,10a-octahydrophenanthrene-3,3(2*H*)-dicarbonitrile (86)**

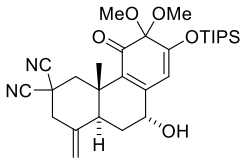


To a solution of **85a** (396 mg, 0.820 mmol) in MeOH/CH_2Cl_2 (5 mL/5 mL, 1/1) was added PIDA (317 mg, 0.984 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 2 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous

$Na_2S_2O_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford the product **86** (410 mg, 98%) as bright yellow oil:

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (1H, br), 5.14 (1H, s), 4.93 (1H, br), 3.72 (1H, dd, *J* = 14.2, 2.3 Hz), 3.36 (3H, s), 3.30 (3H, s), 3.03 (1H, dd, *J* = 13.2, 2.3 Hz), 2.67 (1H, d, *J* = 13.2 Hz), 2.51-2.31 (2H, m), 2.11 (1H, d, *J* = 11.9 Hz), 1.83 (1H, d, *J* = 14.2 Hz), 1.33 (3H, s), 1.32-1.20 (5H, m), 1.12 (18H, d, *J* = 7.5 Hz).

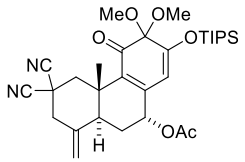
(4a*S,9*R**,10a*S**)-9-hydroxy-6,6-dimethoxy-4a-methyl-1-methylene-5-oxo-7-((triisopropylsilyl)oxy)-1,4,4a,5,6,9,10,10a-octahydrophenanthrene-3,3(2*H*)-dicarbonitrile (88)**



To a stirred solution of **86** (359 mg, 0.704 mmol) in THF (5 mL) was added LiHMDS (1.09M in *n*-hexane, 0.97 mL, 1.05 mmol, 1.5 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution Davis' oxaziridine **87** (368 mg, 1.41 mmol, 2.0 equiv) in THF (3 mL) was added. The reaction mixture was warmed to 0 °C and stirred for 2 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **88** (298 mg, 80%) as yellow oil:

R_f = 0.53 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, s), 5.30 (1H, s), 4.93 (1H, s), 4.23 (1H, br), 3.60 (1H, dd, *J* = 14.2, 2.3 Hz), 3.35 (3H, s), 3.31 (3H, s), 3.05 (1H, dd, *J* = 13.2, 2.3 Hz), 2.72 (1H, d, *J* = 13.2 Hz), 2.36 (1H, dd, *J* = 9.2, 6.4 Hz), 1.95-1.78 (3H, m), 1.35-1.21 (3H, m), 1.30 (3H, s), 1.13 (18H, d, *J* = 7.5 Hz); HRMS-ESI $[M+Na]^+$ calculated for $C_{29}H_{42}N_2NaO_5Si$: 549.2755, found: 549.2758.

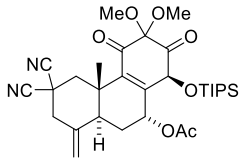
(4a*S,9*R**,10a*S**)-3,3-dicyano-6,6-dimethoxy-4a-methyl-1-methylene-5-oxo-7-((triisopropylsilyl)oxy)-1,2,3,4,4a,5,6,9,10,10a-decahydrophenanthren-9-yl acetate (89)**



To a solution of **88** (27.0 mg, 0.0513 mmol) and DMAP (0.6 mg, 0.0051 mmol, 0.1 equiv) in CH_2Cl_2 (0.5 mL) was added Et_3N (0.014 mL, 0.103 mmol, 2.0 equiv), then Ac_2O (0.0072 mL, 0.0769 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (2 mL). The aqueous layer was extracted with EtOAc (3 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **89** (18.5 mg, 79%) as yellow oil:

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, d, *J* = 4.0 Hz), 5.31 (1H, s), 5.21 (1H, s), 4.91 (1H, s), 3.59 (1H, dd, *J* = 14.3, 2.3 Hz), 3.37 (3H, s), 3.30 (3H, s), 3.06 (1H, dd, *J* = 13.2, 2.3 Hz), 2.73 (1H, d, *J* = 14.3 Hz), 2.37 (1H, d, *J* = 13.2 Hz), 2.08 (3H, s), 1.99-1.80 (3H, m), 1.33 (3H, s), 1.29-1.19 (3H, m), 1.16-1.06 (18H, m); HRMS-ESI $[M+H]^+$ calculated for $C_{31}H_{45}N_2O_6Si$: 569.3041, found: 569.3042.

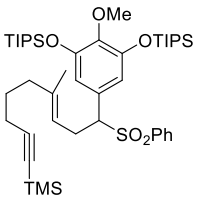
(4a*S,8*S**,9*R**,10a*S**)-3,3-dicyano-6,6-dimethoxy-4a-methyl-1-methylene-5,7-dioxo-8-((triisopropylsilyl)oxy)-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-9-yl acetate (90)**



To a solution of **89** (5.4 mg, 0.0094 mmol) and $NaHCO_3$ (7.9 mg, 0.094mmol, 10 equiv)in CH_2Cl_2 (0.5 mL) was added *m*CPBA (5.0 mg, 0.0188 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with EtOAc (3 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford the product **90** (3.5 mg, 66%) as pale-yellow oil:

R_f = 0.69 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (1H, s), 5.33 (1H, s), 4.93 (1H, br), 3.59 (3H, s), 3.35 (3H, s), 3.11 (1H, dd, *J* = 12.8, 2.3 Hz), 3.05 (1H, dd, *J* = 12.8, 2.3 Hz), 2.74 (1H, d, *J* = 12.8 Hz), 2.39-2.31 (2H, m), 2.11 (3H, s), 2.05-1.83 (2H, m), 1.77-1.68 (1H, m), 1.35 (3H, s), 1.19-1.00 (21H, m).

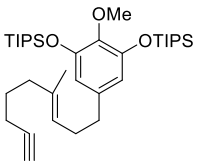
(*E*)-((2-methoxy-5-(4-methyl-1-(phenylsulfonyl)-9-(trimethylsilyl)non-3-en-8-yn-1-yl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (76a)



To a solution of **76** (5.04 g, 8.30 mmol), TBAI (307 mg, 0.830 mmol, 0.1 equiv) and in THF/DMPU (50 mL/10mL, 5/1) was added *n*BuLi (1.64M in *n*-hexane, 0.6.5 mL, 9.13 mmol, 1.1 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. To the stirred solution was added **29** (2.73 g, 9.96 mmol, 1.2 equiv) in THF (5 mL×3) and stirred for 30 min at –78 °C and warmded to rt. After 16 h, to the reaction mixture was added satrurated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **76a** (3.72 g, 53%) as colorless oil:

R_f = 0.63 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.5 Hz), 7.50 (1H, dd, *J* = 8.5, 8.5 Hz), 7.36 (2H, dd, *J* = 8.5, 8.5 Hz), 6.26 (2H, s), 4.83 (1H, t, *J* = 6.9 Hz), 3.80 (1H, dd, *J* = 11.9, 4.0 Hz), 3.73 (3H, s), 3.15 (1H, ddd, *J* = 14.2, 6.9, 4.0 Hz), 2.68 (1H, ddd, *J* = 14.2, 11.9, 6.9 Hz), 2.03 (2H, t, *J* = 7.4 Hz), 1.92 (2H, t, *J* = 7.4 Hz), 1.58 (3H, s), 1.50-1.40 (2H, m), 1.23-1.13 (6H, m), 1.05 (18H, d, *J* = 7.5 Hz), 1.04 (18H, d, *J* = 7.5 Hz), 0.11 (9H, s).

(*E*)-((2-methoxy-5-(4-methylnon-3-en-8-yn-1-yl)-1,3-phenylene)bis(oxy))bis(triisopropylsilane) (98)



To a solution of **76a** (1.81 g, 2.26 mmol) in MeOH (20 mL) was added magnesium turnings (276 mg, 11.3 mmol, 5.0 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C and warm to rt. After 16 h stirring, to the mixture was added saturated 1M HCl solution (2 mL) and stirred until consumption of magnesium. The aqueous layer was extracted with EtOAc (30 mL×3), and the combinded organic layer was dried over Na_2SO_4, and evaporated. The residue was used next step without further purification. R_f = 0.80 (hexane/ethyl acetate = 20/1):

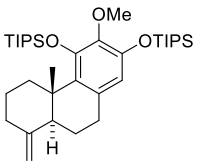
To a crude solution in MeOH (20 mL) was added K_2CO_3 (940 mg, 6.80 mmol, 3.0 equiv) was added, and the reaction mixture was stirred for 1h at room temperature. After disappearance of the

starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (1 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used next step without further purification. R_f = 0.80 and 0.38 (hexane/ethyl acetate = 20/1):

To a solution of crude product in CH_2Cl_2 (20 mL) was added imidazole (308 mg, 4.53 mmol, 2.0 equiv), then TIPSCl (0.72 mL, 3.39 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford the product **85a** (782 mg, 59% over 3 steps) as colorless oil:

R_f = 0.80 (hexane/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (2H, s), 5.16 (1H, t, *J* = 7.5 Hz), 3.74 (3H, s), 2.46 (2H, t, *J* = 7.5 Hz), 2.22 (2H, dt, *J* = 7.5, 7.5 Hz), 2.13 (2H, dt, *J* = 7.5, 2.3 Hz), 2.04 (2H, t, *J* = 7.5 Hz), 1.94 (1H, t, *J* = 2.3 Hz), 1.61 (2H, tt, *J* = 7.5, 7.5 Hz), 1.58 (3H, s), 1.27 (6H, qq, *J* = 7.5, 7.5 Hz), 1.10 (36H, d, *J* = 7.5 Hz).

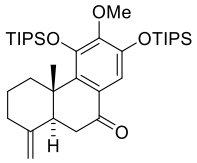
(((4b*S,8a*S**)-3-methoxy-4b-methyl-8-methylene-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2,4-diyl)bis(oxy))bis(triisopropylsilane) (99)**



To a suspension of indium tribromide (130 mg, 0.367 mmol, 0.2 equiv) in CH_2Cl_2 (2 mL) was added **98** (1.08 g, 1.84 mmol) in CH_2Cl_2 (1 mL×3) at –20 °C, and the reaction mixture was stirred for 3 h at –20 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford the product **99** (897 mg, 83%) as colorless oil:

R_f = 0.90 (hexane/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (1H, s), 4.81 (1H, s), 4.54 (1H, s), 3.77 (3H, s), 3.27 (1H, ddd, *J* = 13.0, 4.0, 4.0 Hz), 2.81 (1H, ddd, *J* = 18.7, 10.2, 6.3 Hz), 2.66 (1H, dd, *J* = 18.7, 4.0 Hz), 2.35 (1H, ddd, *J* = 13.0, 2.3, 2.3 Hz), 2.13-2.03 (2H, m), 1.72-1.57 (3H, m), 1.42 (3H, qq, *J* = 7.5, 7.5 Hz), 1.34-1.18 (5H, m), 1.15-1.03 (39H, m).

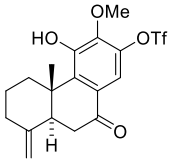
(4a*S,10a*S**)-6-methoxy-4a-methyl-1-methylene-5,7-bis((triisopropylsilyl)oxy)-2,3,4,4a,10,10a-hexahydrophenanthren-9(*1H*)-one (100)**



To a stirred solution of **99** (45.0 mg, 0.0766 mmol) in *t*BuOH (1 mL) was added CuCl (0.8 mg, 0.0077 mmol, 3.0 equiv), TBHP (5.5M in decane, 0.070 mL, 0.383 mmol, 5.0 equiv) at room temperature, and the reaction mixture was stirred for 24 h at 50 °C. After strirring, to the reaction mixture was added $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with Et_2O (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **100** (31.7 mg, 69%) as colorless oil:

R_f = 0.67 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, s), 4.91 (1H, br), 4.56 (1H, br), 3.88 (3H, s), 3.39 (1H, d), 2.70-2.45 (3H, m), 2.38 (1H, d, *J* = 10.7 Hz), 2.15-2.00 (1H, m), 1.86 (1H, d, *J* = 10.7 Hz), 1.79-1.65 (2H, m), 1.47-1.26 (6H, m), 1.25 (3H, s), 1.18-0.99 (36H, m).

(4b*S,8a*S**)-4-hydroxy-3-methoxy-4b-methyl-8-methylene-10-oxo-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl trifluoromethanesulfonate (101)**



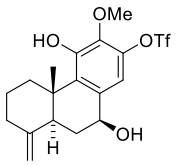
To a stirred solution of **100** (46.4 mg, 0.0772 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (1.0M in THF, 0.23 mL, 0.232 mmol, 3.0 equiv), and the reaction mixture was stirred for 30 min at room temperature. After disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (150 mL×3), and the combined organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification: R_f = 0.12 (hexane/ethyl acetate = 4/1);

To a solution of crude diol (0.0722 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (0.018 mL, 0.1544 mmol, 2.0 equiv), then Tf_2O (0.032 mL, 0.232 mmol, 3.0 equiv) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (3 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and

evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford the product **101** (19.1 mg, 63% over 2 steps) as colorless oil:

R_f = 0.75 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, s), 6.27 (1H, s), 4.96 (1H, s), 4.59 (1H, s), 4.02 (3H, s), 3.24 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.77-2.54 (3H, m), 2.41 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.09 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.86-1.69 (2H, m), 1.48 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.26 (3H, s).

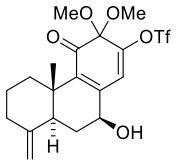
(4b*S,8a*S**,10*S**)-4,10-dihydroxy-3-methoxy-4b-methyl-8-methylene-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl trifluoromethanesulfonate (101a)**



To a solution of **101** (17.8 mg, 0.0423 mmol) in MeOH (1mL) was added sodium borohydride (3.2 mg, 0.0846 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 5 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1 to 5/1) to afford the product **101a** (17.0 mg, 95%) as colorless oil:

R_f = 0.68 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, s), 6.12 (1H, s), 4.88 (1H, s), 4.80-4.69 (1H, m), 4.59 (1H, s), 3.92 (3H, s), 3.09 (1H, ddd, *J* = 13.1, 4.1, 4.1 Hz), 2.37 (1H, ddd, *J* = 13.1, 4.1, 4.1 Hz), 2.26 (2H, d, *J* = 13.1 Hz), 2.17 (1H, dd, *J* = 13.1, 6.3 Hz), 2.12-2.01 (1H, m), 1.85-1.53 (3H, m), 1.42-1.27 (1H, m) , 1.18 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{18}H_{21}F_3NaO_6S$: 445.1, found: 445.1.

(4b*S,8a*S**,10*S**)-10-hydroxy-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthren-2-yl trifluoromethanesulfonate (102)**

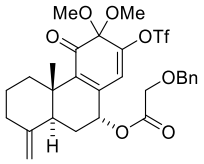


To a solution of **101a** (21.4 mg, 0.0507 mmol) in MeOH/CH_2Cl_2 (0.5 mL/0.5 mL, 1/1) was added PIDA (19.5 mg, 0.0607 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $Na_2S_2O_3$ solution (5mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the

combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 1/0 to 5/1) to afford the product **102** (18.9 mg, 79%) as bright yellow oil:

R_f = 0.33 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, s), 4.88 (1H, br), 4.54 (1H, br), 4.48-4.38 (1H, m), 3.34 (3H, s), 3.31 (3H, s), 2.50 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.40-2.29 (1H, m), 2.19 (1H, ddd, *J* = 13.1, 6.3, 2.3 Hz), 2.15 (1H, d, *J* = 13.1 Hz), 1.99 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.79 (1H, d, *J* = 6.3 Hz), 1.74-1.51 (2H, m), 1.37-1.28 (2H, m), 1.13 (3H, s).

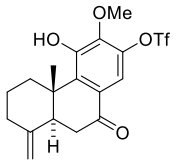
(4a*S,9*R**,10a*S**)-6,6-dimethoxy-4a-methyl-1-methylene-5-oxo-7-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4,4a,5,6,9,10,10a-decahydrophenanthren-9-yl 2-(benzyloxy)acetate (104)**



To a solution of **102** (18.9 mg, 0.0394 mmol), **103** (13.1 mg, 0.0788 mmol, 2.0 equiv) and triphenylphosphine (20.7 mg, 0.0788 mmol, 2.0 equiv) in THF (1 mL) was added DEAD (2.2M in toluene, 0.036 mL, 0.0788 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $Na_2S_2O_3$ solution (3 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **104** as bright yellow oil quantitatively:

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (5H, m), 6.09 (1H, s), 5.63 (1H, dd, *J* = 2.3, 2.3 Hz), 4.89 (1H, br), 4.69-4.61 (3H, m), 4.16 (2H, s), 3.43 (3H, s), 3.35 (3H, s), 2.44 (1H, ddd, *J* = 13.1, 4.0, 4.0 Hz), 2.39-2.31 (1H, m), 2.25 (1H, dd, *J* = 8.0, 4.0 Hz), 2.01 (1H, ddd, *J* = 13.1, 13.1, 6.0 Hz), 1.93-1.84 (1H, m), 1.77-1.56 (3H, m), 1.34-1.16 (1H, m), 1.05 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{31}F_3NaO_9S$: 623.2, found: 623.2.

(4b*S,8a*S**)-4-hydroxy-3-methoxy-4b-methyl-8-methylene-10-oxo-4b,5,6,7,8,8a,9,10-octahydrophenanthren-2-yl trifluoromethanesulfonate (101)**

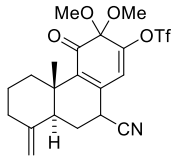


To a stirred solution of **102** (7.8 mg, 0.0171 mmol) in toluene (0.5 mL) was added KCN (3.3 mg, 0.0513 mmol, 3.0 equiv) and dibenzo 18-crown-6 (18.4 mg, 0.0513 mmol, 3.0 equiv) at room

temperature. The mixture was stirred for 14 h at room temperature. After disappearance of the starting material, to the solution was added saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with Et_2O (10 mL×2), and the combined organic layer was washed with H_2O (5 mL×2), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **101** as colorless oil quantitatively:

The data of ^1H NMR was described above.

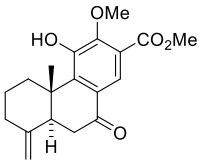
(4b*S,8a*S**)-10-cyano-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthren-2-yl trifluoromethanesulfonate (107)**



To a stirred solution of **104** (13.8 mg, 0.0306 mmol) in toluene (0.5 mL) was added Et_2AlCN (1.0M in toluene, 0.092 mL, 0.0918 mmol, 3.0 equiv) at room temperature. The mixture was stirred for 8 h at room temperature. After disappearance of the starting material, to the solution was added saturated aqueous Rochelle salt solution (2 mL) and stirred for 2 h. The aqueous layer was extracted with Et_2O (10 mL×2), and the combined organic layer was washed with H_2O (5 mL×2), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **107** (35.0 mg, 68%) as colorless oil:

R_f = 0.52 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (1H, dd, *J* = 4.6, 4.6 Hz), 6.22 (1H, s), 4.93 (1H, s), 4.64 (1H, s), 3.71 (3H, s), 3.42 (3H, s), 2.4-2.21 (4H, m), 2.13-1.92 (2H, m), 1.83-1.71 (1H, m), 1.65-1.59 (2H, m), 1.10 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{20}H_{22}F_3NNaO_3$:S: 481.1, found: 481.4.

methyl (4b*S,8a*S**)-4-hydroxy-3-methoxy-4b-methyl-8-methylene-10-oxo-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2-carboxylate (108)**

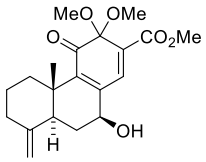


To a stirred solution of **101** (55.0 mg, 0.131 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10.6 mg, 0.0131 mmol, 0.1 equiv) in MeOH (2 mL) was Et_3N (0.054 mL, 393 mmol, 3.0 equiv) at room temperature and filled with CO gas. The mixture was stirred for 12 h at 70 °C under CO atmosphere (1 atm). After

disappearance of the starting material, the reaction vessel was filled with argon. Then, to the solution was added NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layer was washed with H_2O (5 mL×2), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **108** (35.0 mg, 80%) as colorless oil:

R_f = 0.53 (hexane/ethyl acetate = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, s), 6.48 (1H, s), 4.95 (1H, br), 4.59 (1H, br), 3.97 (3H, s), 3.93 (3H, s), 3.29 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.75-2.58 (3H, m), 2.40 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.09 (H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.86-1.69 (2H, m), 1.48 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.27 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{19}H_{22}NaO_5$: 353.1, found: 353.1.

methyl
(4b*S,8a*S**,10*S**)-10-hydroxy-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthrene-2-carboxylate (109)**



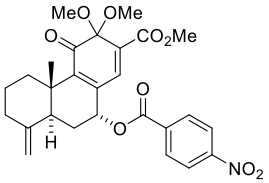
To a solution of **108** (68.9 mg, 0.209 mmol) in MeOH (2 mL) was added sodium borohydride (15.7 mg, 0.417 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 10 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was used for the next reaction without further purification: R_f = 0.35 (hexane/ethyl acetate = 2/1);

To a solution of crude alcohol (0.209 mmol) in MeOH/CH_2Cl_2 (1 mL/1 mL, 1/1) was added PIDA (80.5 mg, 0.250 mmol, 1.2 equiv) at 0 °C, and the reaction mixture was stirred for 10 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous $Na_2S_2O_3$ solution (3 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 1/0 to 3/1) to afford the product **109** (75.4 mg, 100% over 2 steps) as bright yellow oil:

R_f = 0.10 (hexane/ethyl acetate = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, s), 4.88 (1H, s), 4.55 (1H, s), 4.49 (1H, dd, *J* = 109, 6.9 Hz), 3.83 (3H, s), 3.34 (3H, s), 3.20 (3H, s), 2.47 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.38-2.30 (1H, m), 2.21 (1H, ddd, *J* = 13.1, 6.9, 2.3 Hz), 2.15 (1H, d, *J* = 13.1 Hz), 1.99 (1H, ddd, *J* = 13.1, 13.1, 6.9 Hz), 1.83-1.50 (3H, m), 1.30-1.19 (1H, m), 1.18 (3H, s).

methyl

(4b*S,8a*S**,10*R**)-3,3-dimethoxy-4b-methyl-8-methylene-10-((4-nitrobenzoyl)oxy)-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthrene-2-carboxylate (109a)**

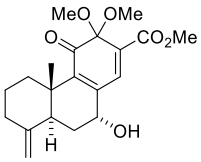


To a solution of **109** (75.6 mg, 0.209 mmol), 4-nitrobenzoic acid (69.7 mg, 0.417 mmol, 2.0 equiv) and triphenylphosphine (109 mg, 0.417 mmol, 2.0 equiv) in THF (2 mL) was added DEAD (2.2M in toluene, 0.18 mL, 0.417 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $Na_2S_2O_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 1/0 to 5/1) to afford the product **109a** (98.8 mg, 93%) as bright yellow oil:

R_f = 0.58 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (2H, d, *J* = 8.7 Hz), 8.22 (2H, d, *J* = 8.7 Hz), 7.09 (1H, s), 5.81 (1H, dd), 4.90 (1H, br), 4.53 (1H, br), 3.79 (3H, s), 3.40 (3H, s), 3.24 (3H, s), 2.51 (1H, ddd, *J* = 13.1, 3.7, 3.7 Hz), 2.41-2.30 (2H, m), 2.11-1.93 (3H, m), 1.85-1.60 (2H, m), 1.37 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.14 (3H, s).

methyl

(4b*S,8a*S**,10*R**)-10-hydroxy-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthrene-2-carboxylate (110)**

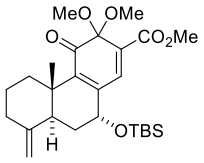


To a solution of **109a** (93.4 mg, 0.183 mmol) in MeOH (2 mL) was added K_2CO_3 (50.4 mg, 0.365 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **110** (56.9 mg, 86%) as bright yellow oil:

R_f = 0.23 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, s), 4.89 (1H, s), 4.54 (1H, s), 4.35 (1H, d), 3.83 (3H, s), 3.35 (3H, s), 3.23 (3H, s), 2.48 (1H, ddd, *J* = 13.1, 2.3, 2.3

Hz), 2.36 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.27 (1H, d, *J* = 13.1 Hz), 2.11-1.98 (1H, m), 1.93 (1H, d, *J* = 13.1 Hz), 1.86 (1H, dd, *J* = 13.1, 4.1 Hz), 1.76-1.54 (3H, m), 1.36-1.21 (1H, m), 1.07 (3H, s).

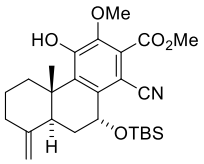
methyl (4b*S,8a*S**,10*R**)-10-((tert-butyldimethylsilyl)oxy)-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthrene-2-carboxylate (111)**



To a solution of **110** (15.2 mg, 0.0419 mmol) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (0.015 mL, 0.123 mmol, 3.0 equiv), then TBSOTf (0.019 mL, 0.0838 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred for 2 h at 0 °C. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **111** as bright yellow oil quantitatively:

R_f = 0.80 (hexane/ethyl acetate = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, s), 4.89 (1H, br), 4.86 (1H, br), 4.31 (1H, dd, *J* = 4.1, 1.3 Hz), 3.83 (3H, s), 3.35 (3H, s), 3.21 (3H, s), 2.48 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.40-2.29 (2H, m), 2.06 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.84-1.57 (4H, m), 1.29 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.05 (3H, s), 0.88 (9H, s), 0.18 (3H, s), 0.14 (3H, s).

methyl (4b*S,8a*S**,10*R**)-10-((tert-butyldimethylsilyl)oxy)-1-cyano-4-hydroxy-3-methoxy-4b-methyl-8-methylene-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2-carboxylate (113)**

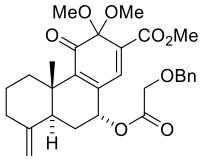


To a stirred solution of **111** (9.2 mg, 0.0192 mmol) in DMF/H_2O (0.5 mL/0.5 mL, 1/1) was added KCN (6.3 mg, 0.0960 mmol, 5.0 equiv) and NH_4Cl (3.8 mg, 0.0576 mmol, 3.0 equiv) at room temperature. The mixture was stirred for 12 h at 80 °C. After disappearance of the starting material, to the solution was added saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with Et_2O (10 mL×2), and the combined organic layer was washed with H_2O (5 mL×2), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **113** (6.7 mg, 75%) as pale-yellow oil

quantitatively:

R_f = 0.20 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, s), 5.12 (1H, dd, *J* = 5.5, 5.5 Hz), 4.87 (1H, s), 4.54 (1H, s), 4.02 (3H, s), 3.90 (3H, s), 3.09 (1H, ddd, *J* = 13.3, 3.2, 3.2 Hz), 2.85 (1H, d, *J* = 13.3 Hz), 2.44-2.35 (1H, m), 2.15-2.04 (1H, m), 1.95 (1H, ddd, *J* = 13.3, 2.3, 2.3 Hz), 1.82-1.69 (3H, m), 1.44 (1H, ddd, *J* = 13.3, 13.3, 5.5 Hz), 1.08 (3H, s), 0.86 (9H, s), 0.24 (3H, s), 0.20 (3H, s); LRMS-ESI $[M+Na]^+$ calculated for $C_{26}H_{37}NNaO_5Si$: 494.2, found: 494.2.

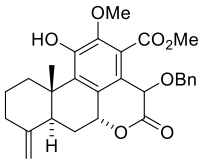
methyl
(4b*S,8a*S**,10*R**)-10-(2-(benzyloxy)acetoxy)-3,3-dimethoxy-4b-methyl-8-methylene-4-oxo-3,4,4b,5,6,7,8,8a,9,10-decahydrophenanthrene-2-carboxylate (114)**



To a solution of **110** (8.8 mg, 0.0243 mmol), **103** (8.1 mg, 0.0485 mmol, 2.0 equiv) and EDCI (9.3 mg, 0.0485 mmol, 2.0 equiv) in CH_2Cl_2 (1 mL) was added DMAP (5.9 mg, 0.0485 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added Hexane (5 mL). The white suspension was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **114** (12.2 mg, 98%) as bright yellow oil:

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m), 7.03 (1H, s), 5.66 (1H, dd, *J* = 4.1, 2.3 Hz), 4.89 (1H, br), 4.64 (2H, s), 4.50 (1H, br), 4.17 (1H, d, *J* = 16.5 Hz), 4.11 (1H, d, *J* = 16.5 Hz), 3.81 (3H, s), 3.34 (3H, s), 3.22 (3H, s), 2.44 (1H, ddd, *J* = 13.1, 2.3, 2.3 Hz), 2.38-2.30 (1H, m), 2.24 (1H, dd, *J* = 13.1, 4.1 Hz), 2.01 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.96-1.82 (2H, m), 1.75-1.61 (2H, m), 1.27 (1H, ddd, *J* = 13.1, 13.1, 6.3 Hz), 1.08 (3H, s); HRMS-ESI $[M+Na]^+$ calculated for $C_{29}H_{34}NaO_8$: 533.2146, found: 533.2148.

methyl
(6a*R,7a*S**,11a*S**)-4-(benzyloxy)-1-hydroxy-2-methoxy-11a-methyl-8-methylene-5-oxo-4,5,6a,7,7a,8,9,10,11,11a-decahydrodibenzo[de,g]chromene-3-carboxylate (116)**

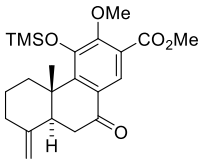


To a stirred solution of **114** (4.0 mg, 0.0078 mmol) in toluene (0.5 mL) was added DBU (0.012 mL, 0.0780 mmol, 10 equiv) at room temperature. The mixture was stirred for 2 h at 50 °C. After

disappearance of the starting material, to the solution was added saturated aqueous NH_4Cl solution (3 mL). The aqueous layer was extracted with Et_2O (10 mL×2), and the combined organic layer was washed with H_2O (5 mL×2), brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1 to 4/1) to afford the product **116** (2.3 mg, 62%) as pale-yellow oil:

R_f = 0.55 (hexane/ethyl acetate = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.28 (5H, m), 6.49 (1H, s), 4.96 (1H, d, *J* = 9.6 Hz), 4.75 (1H, s), 4.60 (1H, d, *J* = 9.6 Hz), 4.41 (1H, s), 3.97 (1H, s), 3.93 (3H, s), 3.85 (3H, s), 3.49-3.18 (2H, m), 2.82-2.55 (3H, m), 2.48-2.32 (1H, m), 2.17-1.94 (1H, m), 1.84-1.72 (2H, m), 1.47 (1H, ddd, *J* = 13.2, 13.2, 5.5 Hz), 1.26 (3H, s) ; LRMS-ESI $[M+Na]^+$ calculated for $C_{28}H_{30}NaO_7$: 501.2, found: 502.2.

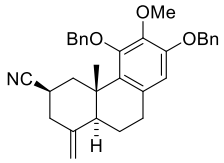
methyl (4b*S,8a*S**)-3-methoxy-4b-methyl-8-methylene-10-oxo-4-((trimethylsilyl)oxy)-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2-carboxylate (108')**



To a stirred solution of **114** (3.9 mg, 0.0076 mmol) in THF (0.5 mL) was added TMSCl (0.2M in THF, 0.11 mL, 0.0228 mmol, 3.0 equiv) and DBU (0.1M in THF, 0.15 mL, 0.0152 mmol, 2.0 equiv) at room temperature. The mixture was stirred for 16 h at room temperature. After disappearance of the starting material, to the solution was added saturated aqueous NH_4Cl solution (3 mL). The aqueous layer was extracted with Et_2O (10 mL×2), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **108'** (2.6 mg, 85%) as pale-yellow oil:

R_f = 0.70 (hexane/ethyl acetate = 2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s), 4.95 (1H, s), 4.58 (1H, s), 4.11 (1H, d, *J* = 5.5 Hz), 3.97 (3H, s), 3.91 (3H, s), 3.35-3.24 (1H, m), 2.78-2.57 (3H, m), 2.44-2.34 (1H, m), 2.16-2.00 (1H, m), 1.83-1.66 (2H, m), 1.47 (1H, ddd, *J* = 12.8, 12.8, 5.5 Hz), 1.28 (3H, s), 2.8 (9H, s).

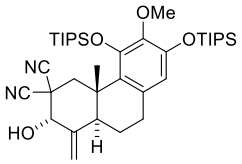
(3*R,4a*S**,10a*S**)-5,7-bis(benzyloxy)-6-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3-carbonitrile (120)**



To a solution of **62d** (290 mg, 0.575 mmol), Bu_3SnH (0.31 mL, 1.15 mmol, 2.0 euqiv) in toluene (5 mL) was added AIBN (18.8 mg, 0.115 mmol, 0.2 equiv) at rt, and the reaction mixture was stirred at 100 °C. After stirring for 36 h, the reaction mixture was concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1 to 10/1) to afford the product **120** as white solid quantitatively (ratio of diastereomer: 15:1):

R_f = 0.48 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 7.3 Hz), 7.50-7.28 (8H, m), 6.49 (1H, s), 5.27 (1H, d, *J* = 11.0 Hz), 5.13 (1H, br), 5.09 (2H, d, *J* = 2.8 Hz), 5.07 (1H, d, *J* = 11.0 Hz), 4.84 (1H, s), 3.83 (3H, s), 3.53 (1H, d, *J* = 13.7 Hz), 3.03 (1H, dd, *J* = 7.3, 7.3 Hz), 2.94-2.72 (2H, m), 2.61 (1H, d, *J* = 13.7 Hz), 2.37 (1H, dd, *J* = 13.7, 7.3Hz), 2.11 (1H, d, *J* = 13.7Hz), 1.84-1.59 (3H, m), 1.47 (3H, s); HRMS-ESI $[M+Na]^+$ calculated for $C_{32}H_{33}NNaO_3$: 502.2353, found: 502.2353.

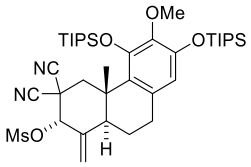
(2S,4aS,10aR)-2-hydroxy-6-methoxy-4a-methyl-1-methylene-5,7-bis((triisopropylsilyl)oxy)-1,4,4a,9,10,10a-hexahydrophenanthrene-3,3(2*H*)-dicarbonitrile (122)



To a solution of **79** (977 mg, 1.53 mmol) in THF (20 mL) was added selenium dioxide (340 mg, 3.06 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred for 18 h at reflux temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous Na_2SO_3 solution (10 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **122** (836 mg, 84%) as colorless oil:

R_f = 0.35 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, s), 5.46 (1H, s), 5.10 (1H, s), 4.66 (1H, s), 4.09 (1H, d, *J* = 14.3 Hz), 3.78 (3H, s), 2.89 (1H, ddd, *J* = 18.9, 12.3, 7.5 Hz), 2.75 (1H, br), 2.73 (1H, br), 2.52 (1H, br), 2.31 (1H, d, *J* = 14.3 Hz), 1.80-1.63 (2H, m), 1.46 (3H, tt, *J* = 7.5, 7.5 Hz), 1.41 (3H, s), 1.25 (3H, tt, *J* = 7.5, 7.5 Hz), 1.19-1.06 (36H, m).

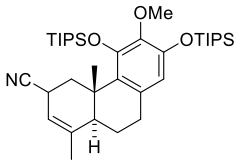
(2S,4aS,10aR)-3,3-dicyano-6-methoxy-4a-methyl-1-methylene-5,7-bis((triisopropylsilyl)oxy)-1, 2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl methanesulfonate (126)



To a solution of **122** (695 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.30 mL, 2.13 mmol, 2.0 equiv), MsCl (0.12 mL, 1.60 mmol, 1.5 equiv) at 0 °C subsequently, and the reaction mixture was stirred for 5 h at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford the product **126** (744 mg, 96%) as colorless oil:

R_f = 0.35 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (1H, s), 5.69 (1H, s), 5.41 (1H, s), 5.31 (1H, s), 4.24 (1H, d, *J* = 14.3 Hz), 3.79 (3H, s), 3.14 (3H, s), 2.91 (1H, ddd, *J* = 17.2, 9.2, 9.2 Hz), 2.77 (1H, ddd, *J* = 17.2, 3.5, 3.5 Hz), 2.66 (1H, dd, *J* = 6.9, 6.9 Hz), 2.25 (1H, d, *J* = 14.3 Hz), 1.80-1.72 (1H, m), 1.46 (3H, tt, *J* = 7.5, 7.5 Hz), 1.43 (3H, s), 1.31-1.20 (3H, m), 1.20-1.03 (36H, m); HRMS-ESI $[M+Na]^+$ calculated for $C_{38}H_{62}N_2NaO_6SSi_2$: 753.3759, found: 753.3761.

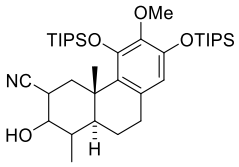
(4aS,10aS)-6-methoxy-1,4a-dimethyl-5,7-bis((triisopropylsilyl)oxy)-3,4,4a,9,10,10a-hexahydro phenanthrene-3-carbonitrile (127)



To a solution of **126** (99.2 mg, 0.135 mmol) in THF (5 mL) was added lithium naphthalenide (0.5M in THF, 1.3 mL, 0.678 mmol, 5.0 equiv) at 0 °C until colored deep-blue. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous NH_4Cl solution (mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 25/1) to afford the product **127** (40.2 mg, 48%) as colorless oil:

R_f = 0.85 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, s), 5.46 (1H, s), 4.27 (1H, d, *J* = 5.7 Hz), 3.77 (3H, s), 3.72 (1H, ddd, *J* = 14.3, 14.3, 14.3 Hz), 3.44-3.33 (1H, m), 2.90-2.67 (2H, m), 2.28-2.10 (1H, m), 1.99 (1H, dd, *J* = 14.3, 5.7 Hz), 1.78 (3H, s), 1.77-1.68 (1H, m), 1.52-1.20 (6H, m), 1.38 (3H, s), 1.20-1.00 (36H, m).

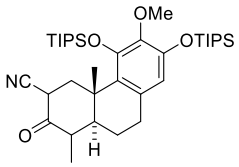
(4aS,10aS)-2-hydroxy-6-methoxy-1,4a-dimethyl-5,7-bis((triisopropylsilyl)oxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3-carbonitrile (129)



To a solution of **127** (99.2 mg, 0.162 mmol) in THF (1.5 mL) was added borane tetrahydrofuran complex (0.94M in THF, 0.51 mL, 0.486 mmol, 3.0 equiv) at 0 °C, and the reaction mixture was stirred for 3 h at 0 °C. After stirring, to the reaction mixture was added AcOH (1 mL), 30% H_2O_2 (1 mL) and stirred for 16 at room temperature. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous Na_2SO_3 solution (3 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **129** (72.9 mg, 71%) as colorless oil:

R_f = 0.22 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (1H, s), 3.98 (1H, dd, *J* = 9.6, 6.4 Hz), 3.78 (3H, s), 2.99 (1H, dd, *J* = 14.2, 9.6 Hz), 2.86 (1H, ddd, *J* = 9.6, 9.6, 7.3 Hz), 2.81-2.63 (2H, m), 2.26 (1H, dd, *J* = 14.2, 7.3 Hz), 2.01-1.87 (2H, m), 1.75 (1H, dddd, *J* = 14.2, 14.2, 14.2, 6.4 Hz), 1.59-1.49 (1H, m), 1.42 (3H, tt, *J* = 7.5, 7.5 Hz), 1.42 (3H, s), 1.31-1.18 (3H, m), 1.21 (3H, s), 1.18-1.04 (36H, m); HRMS-ESI $[M+Na]^+$ calculated for $C_{36}H_{63}NNaO_4Si_2$: 652.4188, found: 652.4186.

(4aS,10aS)-6-methoxy-1,4a-dimethyl-2-oxo-5,7-bis((triisopropylsilyl)oxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3-carbonitrile (130)

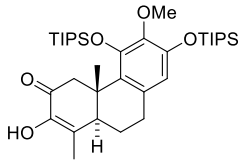


To a solution of **129** (59.8 mg, 0.0949 mmol) in CH_2Cl_2 (2.5 mL) was added DMP (60.3 mg, 0.190 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred for 1 h. After disappearance of the starting material, to the reaction mixture was added satrurated aqueous Na_2SO_3 solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the product **130** (52.8 mg, 89%) as colorless oil:

R_f = 0.25 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (1H, s), 3.78 (3H, s), 3.72 (1H, d, *J* = 16.0 Hz), 2.88-2.65 (2H, m), 2.61-2.51 (1H, m), 2.13 (1H, dd, *J* = 16.0, 2.3 Hz),

1.90 (1H, ddd, *J* = 12.4, 6.4, 2.3 Hz), 1.83-1.51 (3H, m), 1.44 (3H, tt, *J* = 7.5, 7.5 Hz), 1.29 (3H, s), 1.28-1.19 (6H, m), 1.18-1.03 (36H, m).

(4aS,10aR)-2-hydroxy-6-methoxy-1,4a-dimethyl-5,7-bis((triisopropylsilyl)oxy)-4a,9,10,10a-tetrahydrophenanthren-3(4*H*)-one (132)



To a stirred solution of **130** (7.6 mg, 0.0121 mmol) in THF (0.5 mL) was added LDA (0.2M in THF, 0.067 mL, 0.0133 mmol, 1.1 equiv) at –78 °C, and the reaction mixture was stirred for 30 min at –78 °C. Then, to a stirred solution Davis' oxaziridine **131** (5.5 mg, 0.0181 mmol, 1.5 equiv) in THF (1 mL) was added. The reaction mixture was stirred for 1 h at –78 °C. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (100 mL) at –78 °C and stirred further 16 h at room temperature. The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford the product **132** (5.2 mg, 70%) as colorless oil:

R_f = 0.30 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, s), 6.08 (1H, s), 4.31 (1H, d, *J* = 16.5 Hz), 3.77 (3H, s), 2.89 (1H, ddd, *J* = 16.5, 12.8, 6.9 Hz), 2.78 (1H, d, *J* = 6.9 Hz), 2.74 (1H, dddd, *J* = 12.8, 2.3, 2.3, 2.3 Hz), 2.30 (1H, d, *J* = 16.5 Hz), 2.07 (1H, dd, *J* = 12.8, 6.9 Hz), 1.95 (3H, d, *J* = 2.3 Hz), 1.62 (1H, dddd, *J* = 12.8, 12.8, 12.8, 6.9 Hz), 1.43 (3H, tt, *J* = 7.5, 7.5 Hz), 1.26 (3H, s), 1.26 (3H, tt, *J* = 7.5, 7.5 Hz), 1.18-1.04 (36H, m) ; HRMS-ESI $[M+Na]^+$ calculated for $C_{35}H_{60}NaO_5Si_2$: 639.3871, found: 639.3870.

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