

植物由来の生物活性三環性有機化合物の
化学的研究

平成 20 年度

西濱 悠子

Abbreviation

Ac	acetyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
CCE	constant current electrolysis
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
Et	ethyl
Fuc	fucose
Glc	glucose
HASMC	human aortic smooth muscle cells
IBX	2-iodoxybenzoic acid
IC ₅₀	50% inhibitory concentration of a substance
IPM	imipenem
IR	infrared
<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
MOM	Methoxymethyl
mp	melting point
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ns	4-nitrobenzenesulfonyl
PDGF	platelet-derived growth factor

Ph	phenyl
PIFA	Phenyliodine(III) Bis(trifluoro-acetate)
Pr	propyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	<i>p</i> -toluenesulfonyl
Z	benzyloxycarbonyl

目次

序論	1
本論	
第1章 マンゴスチン類の化学的変換	6
第2章 Megistophylline の合成研究	20
結語	47
Experimental section	49
参考文献	95
謝辞	100

序論

古来より民間伝承薬として用いられてきた植物は多様性に富んだ生物活性を示すことが知られている。例えば生薬として知られるセリ科の植物である **Bupleurum falcatum** Linn の根より製造される柴胡は一般に解熱、鎮痛、消炎作用が知られており、黄疸や肝炎、マラリアの治療に用いられている。その有効成分としては血中コレステロール、トリグリセライド低下作用や脂肪肝改善作用などを示す saikosaponin 類¹⁾や抗硬直作用を有する stigmasterol²⁾などが知られている(Figure 1)。

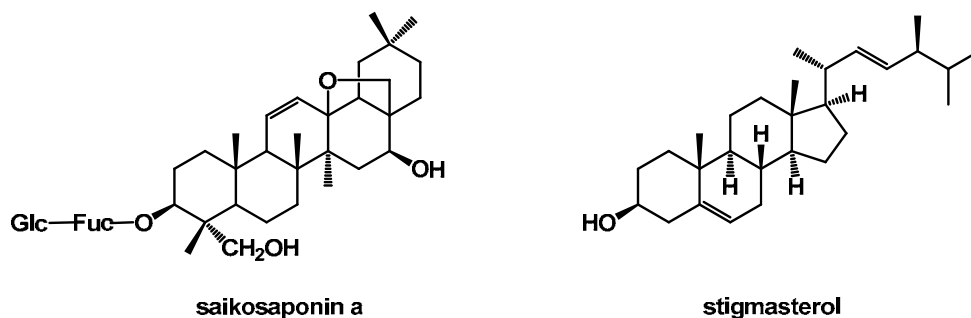


Figure 1

また、ボタン科の植物である *Paeonia lactiflora* Pallas の根である芍薬も生薬として用いられており、鎮痛、抗炎症や平滑筋弛緩作用を有していることが知られ、筋肉の凝りなどに効果がある。有効成分として筋弛緩作用を有している paeoniflorin³⁾や鎮静、解熱、抗痙攣作用を有する paeonol⁴⁾等が含まれていることが知られている(Figure 2)。

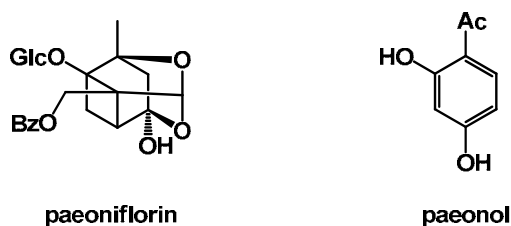


Figure 2

著者らの研究室において、以前オトギリソウ科の植物である *Garcinia mangostana* Lnn.より単離された α -mangostin⁵⁾の全合成研究⁶⁾および構造活性相関研究⁷⁾が行われた(Figure 3)。

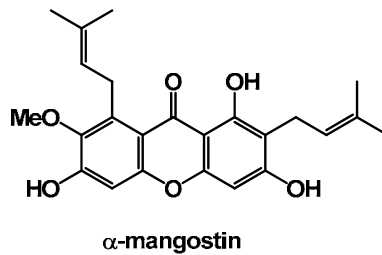


Figure 3

キサントン型化合物である α -mangostin は大変興味深いことに生物活性として抗酸化作用や抗炎症作用だけでなく酸性スフィンゴミエリナーゼ阻害活性⁸⁾や *Helicobacter pylori* に対する抗菌活性⁹⁾など広範囲にわたる特異的な活性を有していることが報告されている。他にも民間伝承薬として用いられてきた植物の中には α -mangostin のような三環性のキサントン骨格やアクリドン骨格などを有する化合物を含んでいることが報告されている。例えば、中国の民間伝承薬であるオトギリソウ科の植物である *Calophyllum membranaceum* はリウマチや関節炎、腰痛、外傷などの治療に用いられてきた。この植物からは数種のキサントン型化合物が単離されており、その中で 2,6-dihydroxy-1,7-dimethoxyxanthone は cyclooxygenase-2 に対する選択的阻害活性を有していることが報告されている¹⁰⁾。また、同様に中国の伝承薬として用いられてきたミカン科の食物である *Severinia buxifolia* Tenore は慢性関節リウマチやマラリア、麻痺、ヘビの咬傷などの治療に用いられてきた。この植物からは数種のアクリドン型化合物が活性成分として単離されており、buxifoliadine B、buxifoliadine D は結腸癌細胞に対して強い細胞毒性を示すことが報告されている¹¹⁾ (Figure 4)。

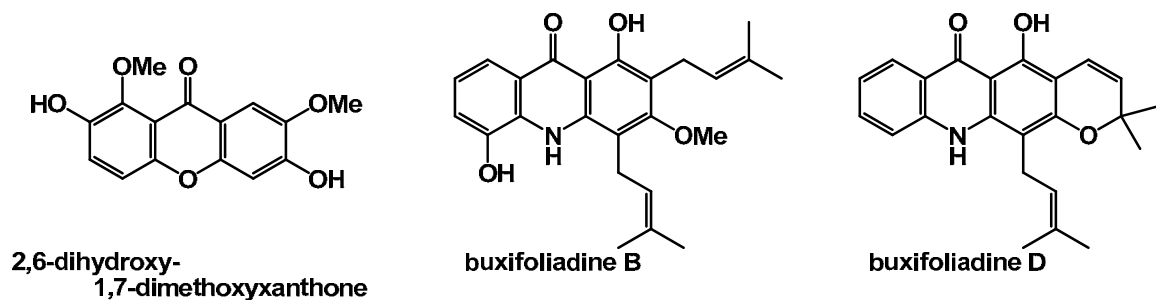


Figure 4

著者らは、このように多様な生物活性を示す植物由来の三環性有機化合物の構造に興味を持ち、このような天然物に関する研究を行い、以下に述べるように本研究を展開した。

まず第1章として、植物由来のキサントン型化合物であるマンゴスチン類の化学的研究について述べる。マンゴスチン類は先に述べたようにオトギリソウ科の植物である *Garcinia mangostana* Lnn.の樹皮や果皮から単離されたキサントン型化合物で、多様かつ特異的な生物活性を有していることが知られている。また、天然から容易かつ大量に入手することが可能であるが、その細胞毒性の強さから直接医薬品として用いることは困難となっている。本研究では天然物であるマンゴスチン類の骨格変換および修飾を行うことで低毒性かつ高生物活性を有するような有用生物活性物質の探索が行えるのではないかと考え、研究を行った。その結果、MRSA (Methicillin-resistant *Staphylococcus aureus*)に対するイミペネムの抗菌作用の増強活性を有する化合物の創製、および、PDGF (Platelet-derived Growth Factor)に誘発される HASMC (Human Aortic Smooth Muscle Cells)増殖抑制活性を有する化合物の創製に成功した。

第2章として、アクリドン型化合物である megistophylline ¹²⁾の合成研究について述べる。Megistophylline はミカン科の植物である *Sarcomelicope megistophylla* Hartlayより単離されたスピロジエノン骨格を有するアクリドン型化合物である。この天然物は第一章で述べる MRSA に対するイミペネムの抗菌作用の増強活性を有する化合物と類似した骨格を有していることから同様の活性を有していることが期待される。ジアリールアミン体を中間体とし、アクリドン誘導体より Claisen 転位反応により megistophylline の全合成を達成した。

本論

第 1 章

マンゴスチン類の化学的変換

1. はじめに

東南アジア原産の植物である *Garcinia mangostana* Lnn. (Guttiferae) は下痢や炎症、潰瘍、皮膚疾患に対する民間薬として用いられてきた。この植物には約40種にのぼるキサントン骨格を有する化合物が含まれていることが知られており、中でもマンゴスチン類は多様な生物活性を有していることが報告されている。例えば α -mangostin は抗酸化作用、抗炎症作用の他に酸性スフィンゴミエリナーゼ阻害活性や *Helicobacter pylori* に対する抗菌活性など、また γ -mangostin にはアロマトラーゼ阻害活性¹³⁾あるいはシクロオキシゲナーゼ阻害活性¹⁴⁾などの多様かつ特異的な生物活性を有している(Figure 5)。

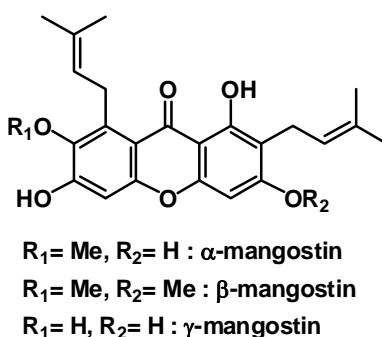


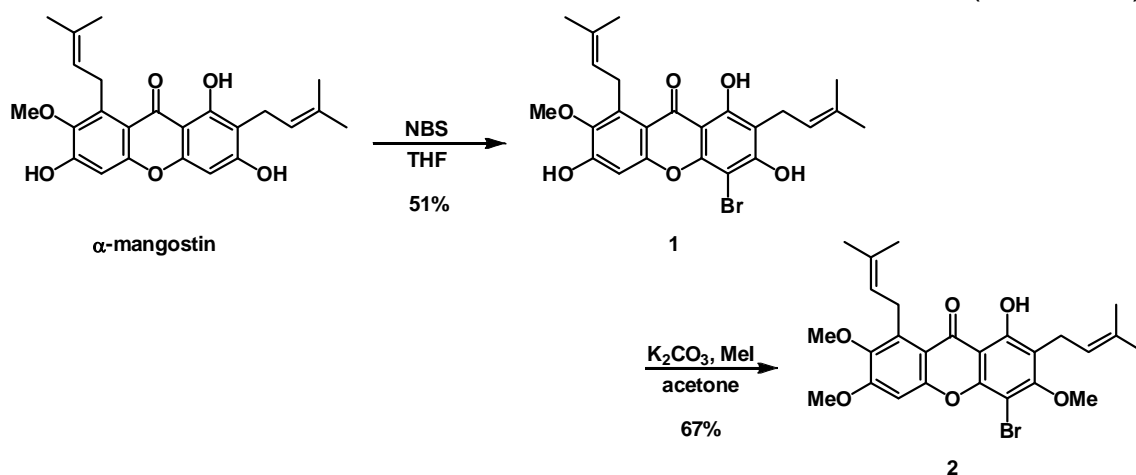
Figure 5

著者らの研究室ではすでに α -mangostin の全合成⁶⁾が達成されており、この骨格に関する合成的知見が蓄積されている。また、マンゴスチン類は容易かつ大量にこの植物の果皮より単離することが可能であることから、天然物を供給源としたマンゴスチン類の誘導体合成を行うことで、効率的な生物活性物質の探索研究の可能性を考案して本研究に着手した。

2. マングスチン類を用いた誘導体合成

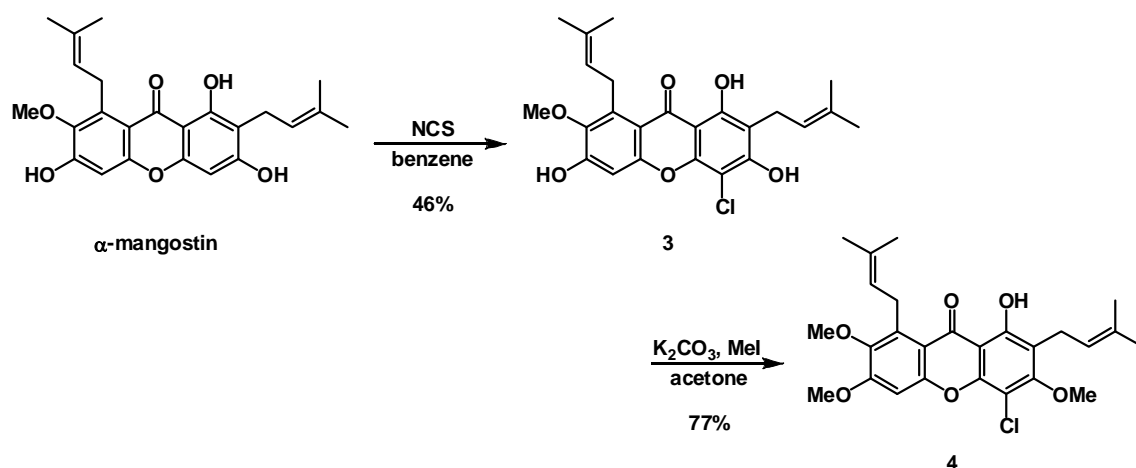
2 - 1 . ハロゲン化によるマングスチン類の変換

はじめに、誘導体合成を行う上で足がかりとなると考えられる芳香環上へのハロゲンの導入を試みた。すなわち、 α -mangostin に対し NBS を作用させることで 4 位選択的に Br の導入された化合物 **1** を得た。得られた **1** の 3 位と 6 位の水酸基をメチルエーテルとして保護することで化合物 **2** へ誘導した(Scheme 1)。



Scheme 1

続いて NCS を用いて同様の反応を行い 4 位に Cl の導入された化合物 **3**、さらに 3 位と 6 位の水酸基をメチルエーテルとして保護した化合物 **4** を合成した (Scheme 2)。



Scheme 2

2 - 2 . 陽極酸化反応を活用したマンゴスチン類の変換¹⁵⁾

続いて、マンゴスチン類にフェノールが多数存在していることから、酸化反応によるマンゴスチン類の誘導体合成を行うこととした。

著者らの研究室では有機電解反応によるフェノール酸化反応を活用した全合成研究が多くなされてきた。有機電解反応とは基質および支持電解質を加えた溶液に電極を浸し、その電極に電流を流すことにより陽極上で酸化反応、陰極上で還元反応が行われる(Figure 6)。

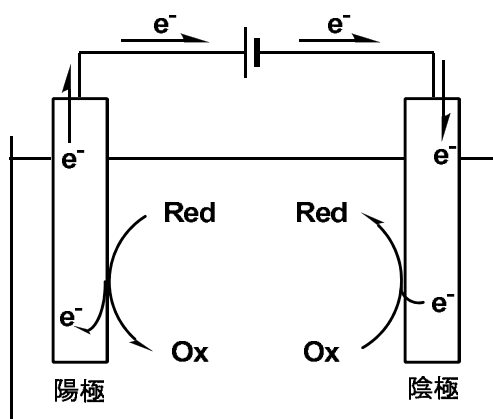
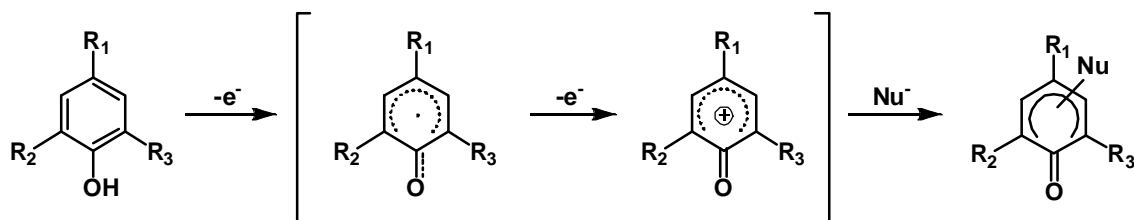


Figure 6

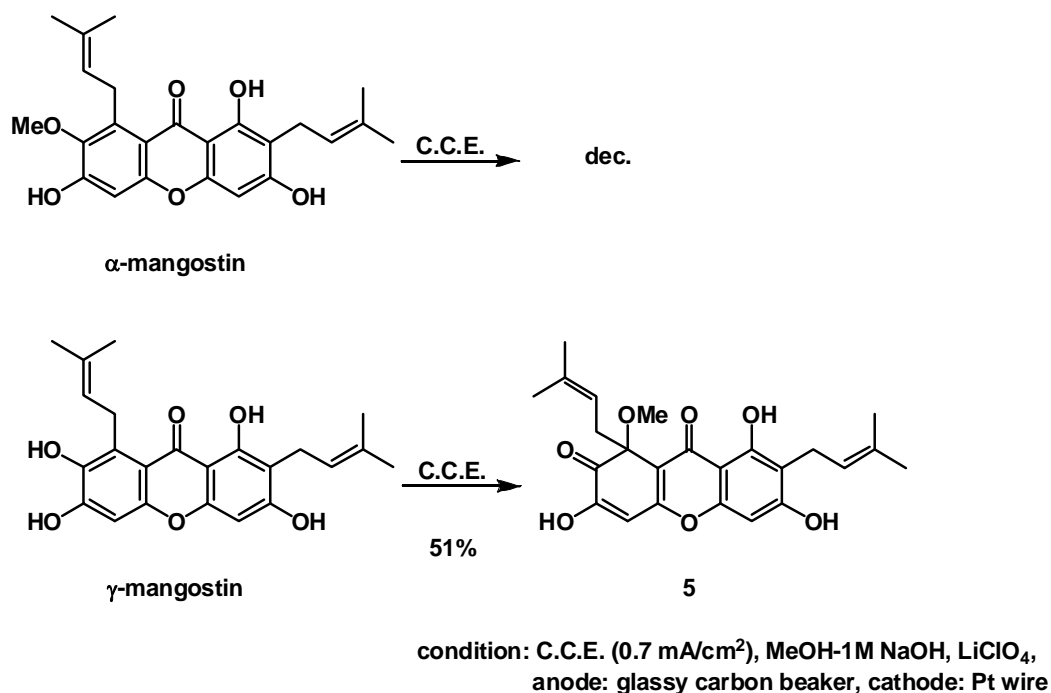
フェノールの陽極酸化反応は、フェノールが二電子酸化されることで本来は求核性を有する芳香核がカチオン活性種となり求電子性を示す(Scheme 3)。



Scheme 3

陽極酸化反応は有害な金属酸化試薬を用いずに酸化反応を行うことができるため、環境調和型の反応であるといえる。また、電極の電位を設定することで選択的な酸化も可能である。マンゴスチン類には多数のフェノールが存在していることから、上記特徴を有する陽極酸化反応はマンゴスチン類の酸化に適しているのではないかと考え、反応を行うこととした。

最初に、 α -mangostin に対し陽極に Pt wire、陰極に glassy carbon beaker を用いて、定電流 (0.7 mA/cm^2 , 2 F/mol) の条件において陽極酸化反応を試みたところ、反応系は複雑な混合物となり、原料がわずかに回収されるのみで新たな生成物を得ることはできなかった。続いて γ -mangostin に対して同様の反応を行ったところ、7 位が酸化され、8 位のプレニル基の付け根に MeO 基の導入された化合物 **5** を単一の生成物として得ることが出来た(Scheme 4)。



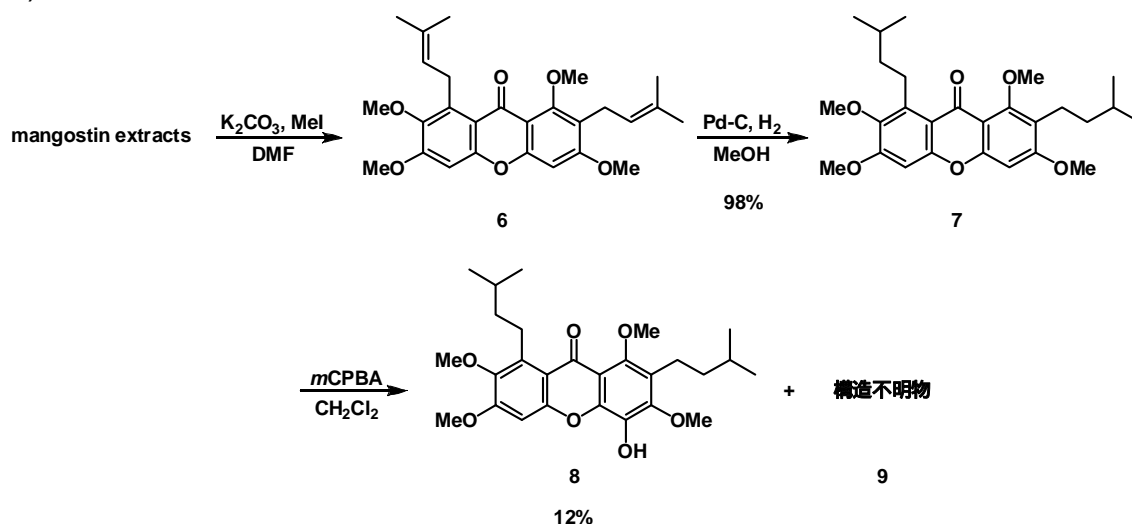
Scheme 4

なお、1 位のフェノールがカルボニル基との水素結合により反応性が抑えられているのに対し、反応性の抑えられていない 3 および 6 位のフェノールがそれぞれカルボニル基に変換されている酸化生成体は見出されていない。このことから 4 位の酸化電位が最も低く、選択的に酸化反応が進行したと考えられる。

2 - 3 . *m*CPBA を用いたマンゴスチン類の変換¹⁶⁾

続いて、*m*CPBA を(*m*-chloroperbenzoic acid)用いた酸化反応について検討を行った。天然物であるマンゴスチン類を本酸化反応に付すと反応点が多数存在することから系中が複雑化することが予想されたので、本実験ではキサントン骨格自体への反応経路を明確とするため、フェノールおよびオレフィンの保護、還元を行った後に酸化反応に付すこととした。 α -mangostin、 γ -mangostin の含まれたマンゴスチン抽出物を DMF 中、炭酸カリウム、ヨウ化メチルの条件に付

し、すべてのフェノールをメチルエーテルとして保護した化合物 **6** を得た。化合物 **6** に対し、接触水素添加反応を行うことでプレニル基のオレフィン部分を飽和し化合物 **7** とした。この化合物を基準として CH_2Cl_2 中 *m*CPBA を用いて酸化反応を行ったところ、反応は複雑な混合物を与えたが、主生成物として 4 位に水酸基の導入された化合物 **8** を収率 12%、および構造不明物 **9** を得た(Scheme 5)。



Scheme 5

化合物 **8** の構造決定に関しては、重水素置換により ^1H NMR スペクトルにおける $\delta 5.65$ のピークが消失したことから新たに水酸基が導入されていることが判明し、またその位置は 3 位の Me 基から 4 位の水酸基に NOE 相関が観測されたことにより決定した(Figure 7)。一方、構造不明物 **9** に対して種々の構造解析を試みたが決定することができないため、誘導体化を考慮して、除去が容易な Bn 基へと変換し、同様の反応を試みることにした。

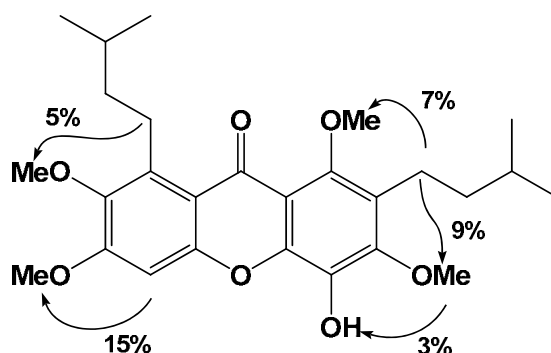
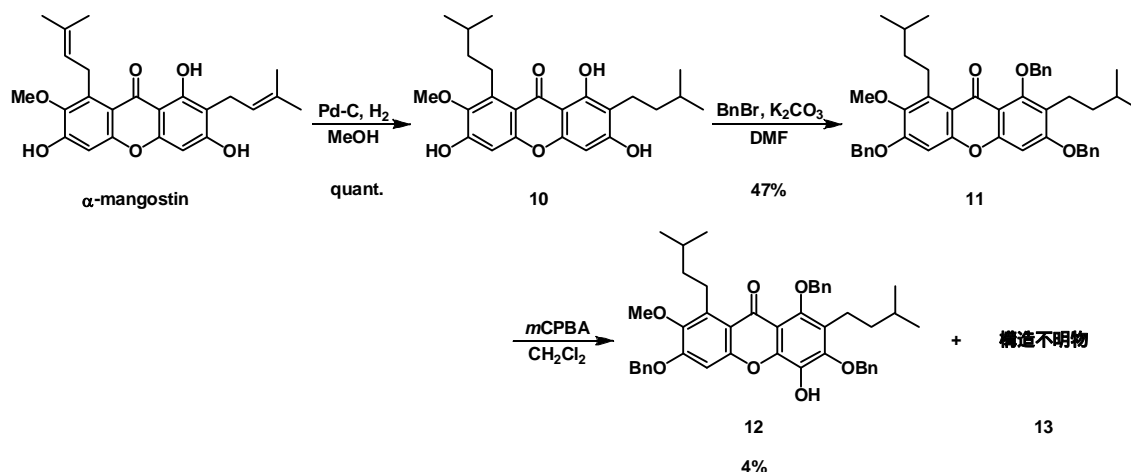


Figure 7

α -Mangostin 中に存在するプレニル基のオレフィンを接触水素添加反応によ

り飽和させた化合物 **10** に対してフェノールを Bn 基で保護し、酸化前駆体 **11** とした。この化合物 **11** に対し化合物 **7** と同様の条件で *m*CPBA と反応させたところ、保護基が Me 基の場合よりも低収率となったが、4 位にヒドロキシル基の導入された化合物 **12** を 4 %、構造不明物 **9** と類似した化合物 **13** を得ることに成功した(Scheme 6)。



Scheme 6

化合物 **12** が化合物 **8** と類似した構造であることは **8** の構造決定時と同様に NOE 測定により決定した(Figure 8)。

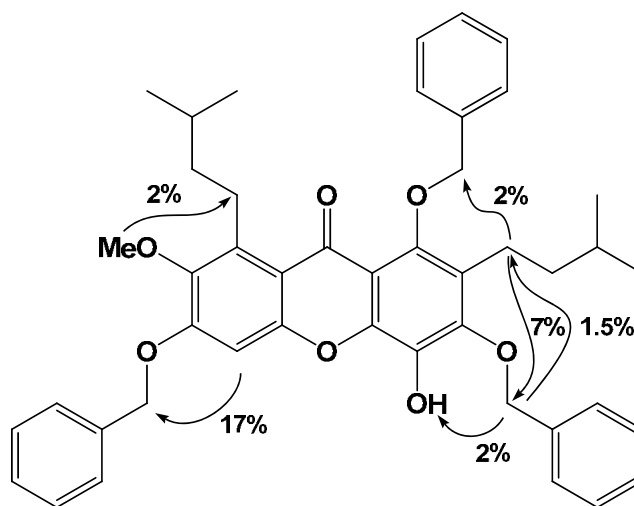


Figure 8

化合物 **13** は固体化したため再結晶溶媒を検討し、その結果トルエン-ヘキサンを用いた系において結晶化したため、X線結晶構造解析により構造決定を行うこととした。その結果、化合物 **13** は右側の芳香環が酸化開裂し Figure 9 に示した構造であることが判明した。

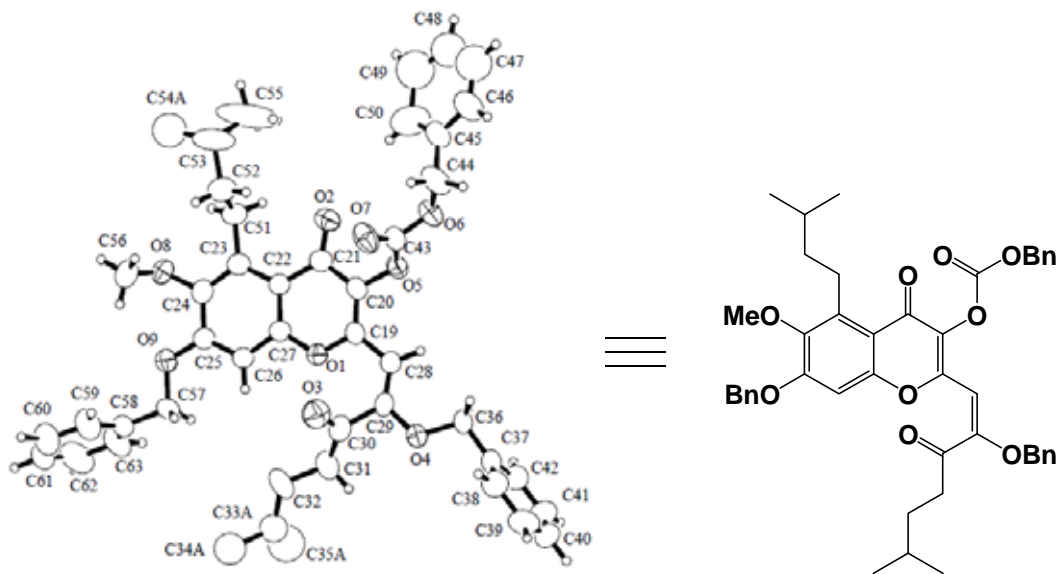


Figure 9

構造不明物 **9** は化合物 **13** と類似した骨格を有していると推定できることから、化合物 **9** は Figure 10 に示した構造を有することが示唆された。

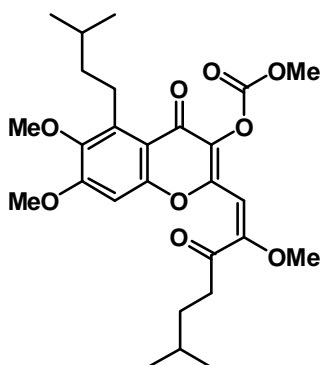
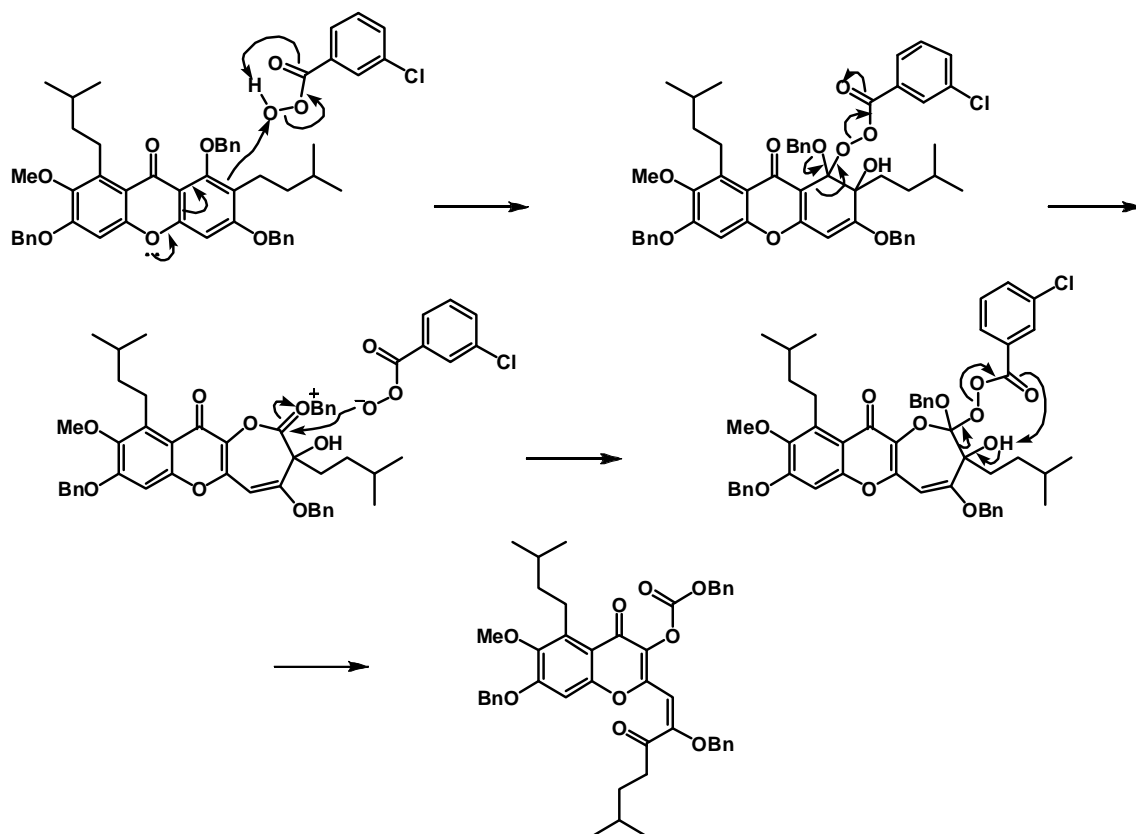


Figure 10

このことから、*m*CPBA を用いた酸化反応の反応機構は次のようであると考えられる (Scheme 7)。すなわち、2 位のアルキル鎖の付け根に *m*CPBA により水酸基が導入され、続いて Baeyer-Villiger 酸化により C-4、C-4' 間に酸素が導入される。さらに酸化されることで C-1、C-2 間の結合が切断され、Figure 10 に示した構造が生成するものと考えられる。



Scheme 7

3 . 生物活性試験

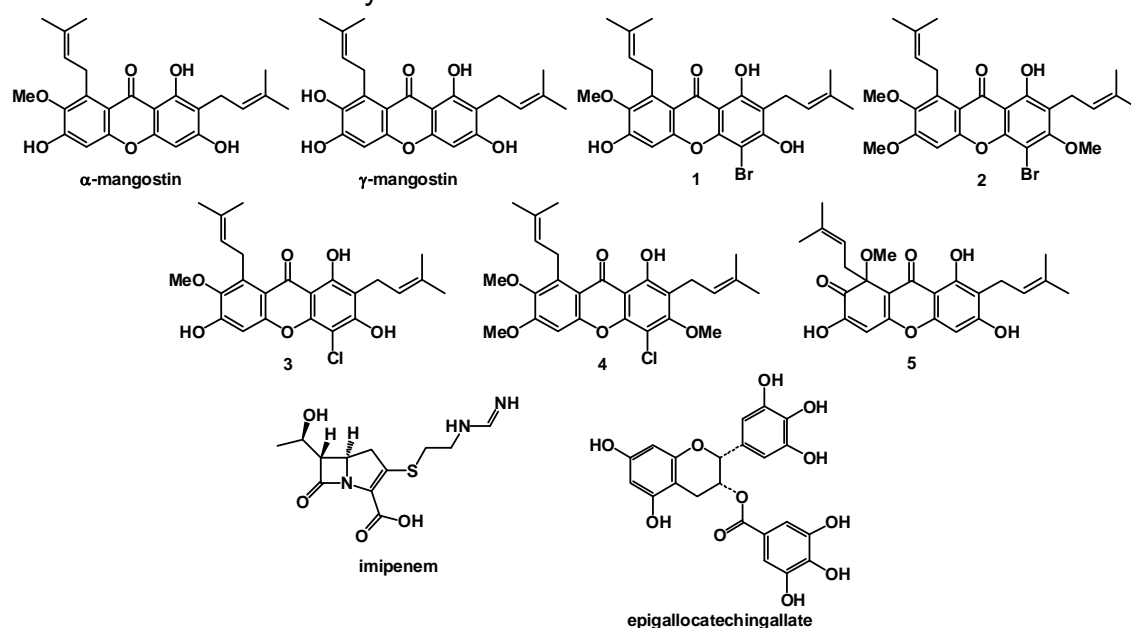
天然物である α -mangostin、 γ -mangostin、および合成したマンゴスチン誘導体に対して抗 MRSA 活性と PDGF に誘発される HASMC 増殖抑制活性について活性試験を行った。

3 - 1 . 抗 MRSA 活性

抗 MRSA 活性について、まず天然物および合成した化合物 1~5 を用いてペーパーディスク法による活性試験を行い、阻止円の大きさにより活性の強さを評価した(Table 1)。MRSA は多数の抗菌剤に対して耐性を有している黄色ブドウ球菌であり、院内感染の原因菌となっている。免疫力の低下している患者に対し日和見感染を起こすこともあるが、抗生物質が効かないため問題となっており、多くの研究者らが抗 MRSA 活性を有する化合物の開発を行っている。生物活性試験の結果、単独では γ -mangostin が中程度の活性を示し、 α -mangostin および化合物 5 は弱い抗 MRSA 活性を示し、他の誘導体については活性を示さ

なかった。さらにイミペネム^{17a-c)}を添加した系においては γ -mangostinの活性値にあまり変化は見られなかったが、 α -mangostin、**5**の活性値は大きくなり、特に化合物**5**においては β -ラクタマーゼ阻害活性を有することが報告されている epigallocatechingallate^{17d)}よりもかなり強い抗菌活性が見られた。このことより α -mangostinと**5**にはイミペネムのMRSAに対する抗菌活性を増強する作用があることが判明した。

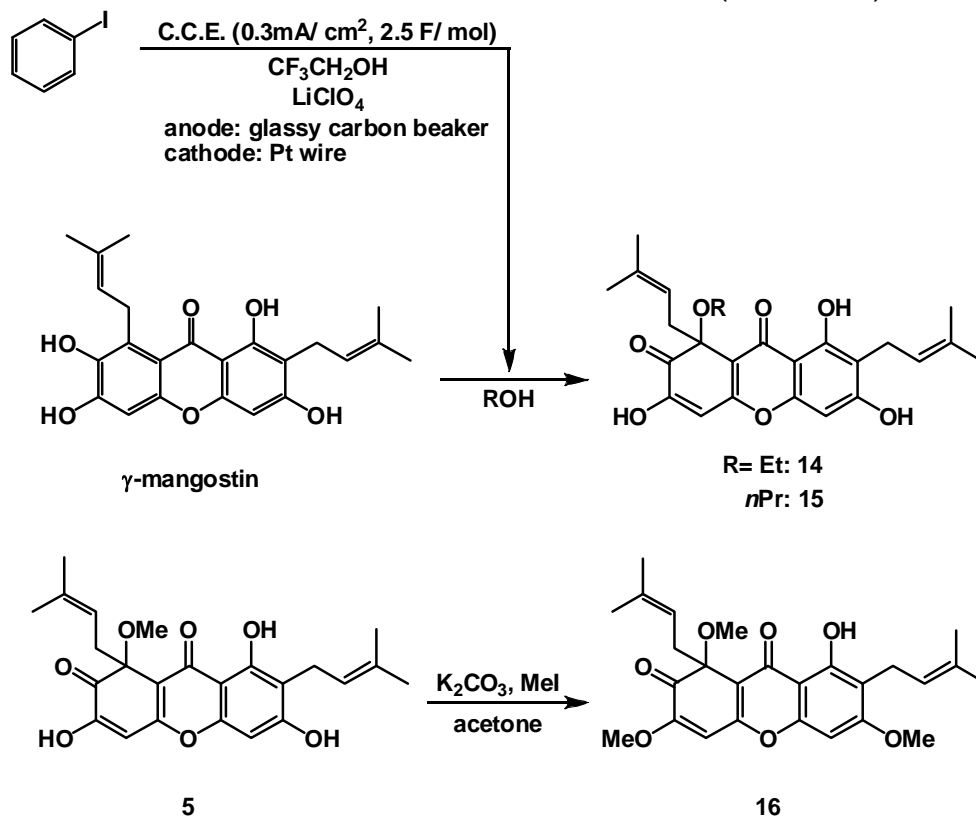
Table 1 anti-MRSA activity



compound	diameter of inhibition zone (mm)	
	IPM-	IPM+
α -mangostin	7	11
γ -mangostin	11	13
1	-	-
2	-	-
3	-	-
4	-	-
5	7	22
IPM	-	-
epigallocatechin-gallate	-	15

paper disk method (10 μ g/ 6 mm disk)

そこで、構造活性相関を視野に入れたさらなる誘導体合成を行い、8位の酸素官能基の炭素鎖を Me から Et、*n*Pr へと変換した化合物 **14**、**15** および化合物 **5** のフェノールを Me 基で保護した化合物 **16** を合成した(Scheme 8)。



Scheme 8

化合物 **14** と **15** の合成にあたり、化合物 **5** と同様に直接陽極酸化反応を用いて酸化を行うことを試みたが、基質の酸化電位が高いため優先的に溶媒が酸化された結果、基質の酸化反応は全く進行しなかった。従って、トリフルオロエタノール中ヨードベンゼンを陽極酸化反応により酸化し、得られた酸化生成体を酸化剤として用いる酸化法¹⁸⁾により目的の化合物 **14** 及び **15** を合成した。これらの化合物 **14** ~ **16** を同様の生物活性試験に付したところ、フェノールを保護した **16** は抗 MRSA 活性を示さず、また、炭素鎖を変化させた化合物 **14** と **15** に関しては単独での抗 MRSA 活性は示さなかったが、イミペネムを添加した系では中程度の抗 MRSA 活性を示した(Table 2)。

Table 2 anti-MRSA activity

compound	diameter of inhibition zone (mm)	
	IPM-	IPM+
14	-	17
15	-	14
16	-	-

paper disk method(10 μ g/ 6 mm disk)

以上により 8 位の酸素官能基の炭素鎖が長いと MRSA に対するイミペネムの抗菌活性を増強する作用が低下し、さらに 3 位と 6 位のフェノールを保護するとその作用が消失することが判明した。

3 - 2 . PDGF に誘発される HASMC 増殖抑制活性¹⁹⁾

続いて PDGF に誘発される HASMC 増殖抑制活性についての活性試験を行った。

アテローム性動脈硬化は動脈の内側に粥状（アテローム性）の隆起（プラーク）が発生する状態のことで、このプラークが成長することによる血流の悪化や、プラークが破れることで血管内で血液が固まり血栓となることで血流を遮断する。アテローム性プラークは血管の内皮が損傷を受けることで単球とよばれる白血球が活性化し、動脈壁を通過して脂肪性細胞へと変化する。PDGF が内膜から与えられると平滑筋細胞が合成型に変化し内膜へと遊走、そこで増殖することでプラークが成長する。

α -mangostin、 γ -mangostin、化合物 1~5、8、9、14~16 に対して行ったところ、*m*CPBA による酸化成績体 8 と 9 に増殖抑制活性が見られた。

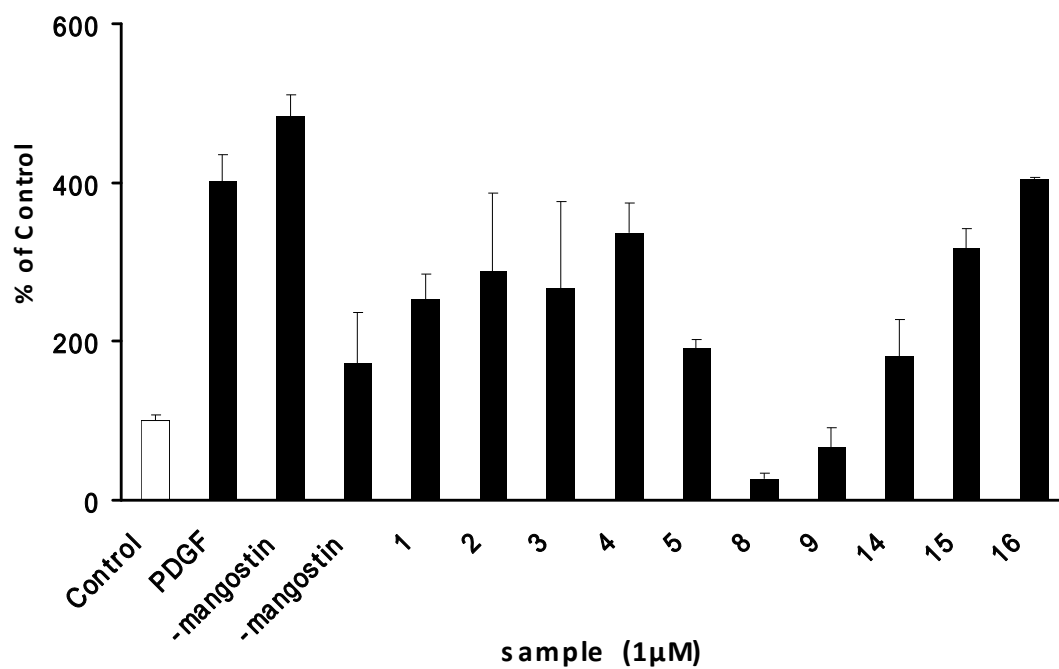


Figure 11

特に活性の強かった化合物 **8** に対して濃度による活性試験を行った。その結果化合物 **8** は濃度依存的な活性値を示し、 IC_{50} は $0.1\mu M$ であった。

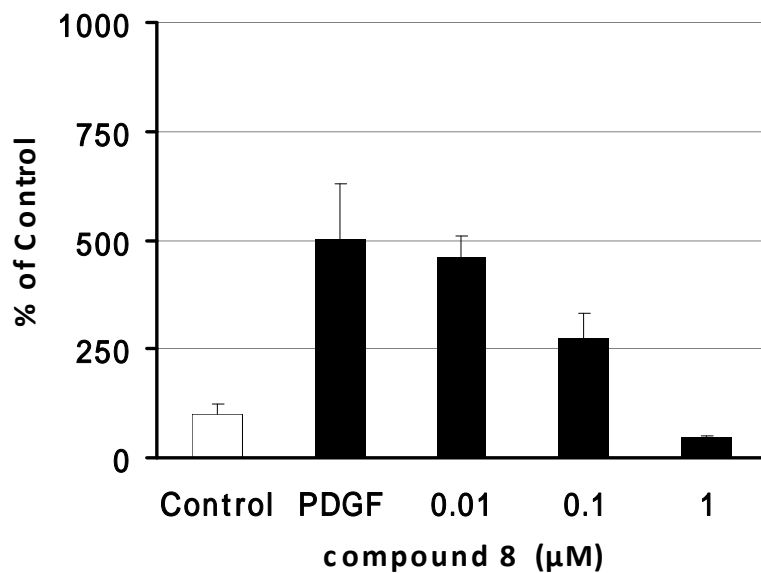


Figure 12

4 . まとめ

マンゴスチン類の誘導体合成を行った結果、MRSA に対するイミペネム[®]の抗菌活性を増強する作用のある化合物 **5** の合成、および PDGF に誘発されるヒト動脈平滑筋細胞増殖抑制活性を有する化合物 **8** の合成を達成した。いずれの化合物も天然物であるマンゴスチン類よりも強力な活性を示したことで、天然物を原料とすることで単段階での有用生物活性物質の探索に成功した。

第 2 章

Megistophylline の合成研究

1. はじめに

Megistophylline¹²⁾は2000年、Papageorugueらによって *Sarcomelicope megistophylla* Hartlay (Rutaceae)の樹皮より単離されたジエノン骨格を含む高度に酸素化されたアクリドン型化合物である (Figure 13)。この植物の樹皮よりグラム陽性菌および陰性菌の両方に対して抗菌活性を示す化合物として megistoquinone と²⁰⁾、さらにアクリドン骨格を有する化合物として melicopicine^{21, 22)}, melicopine²³⁾, melicopidine^{23, 24)}, normelicopidine²⁵⁾, normelicopine²⁶⁾, arborinine²⁷⁾ および1,2,3-trimethoxy-10-methylacridone^{21, 28)}が単離されており、melicopine、normelicopicine、arborinineは抗マラリア活性などを示すことが報告されている²⁹⁾。また、1,2,3-trimethoxy-10-methylacridoneはすでにCoppolaらによってイサト酸無水物を中間体としたアクリドン骨格構築法を用いて全合成が達成されている³⁰⁾。

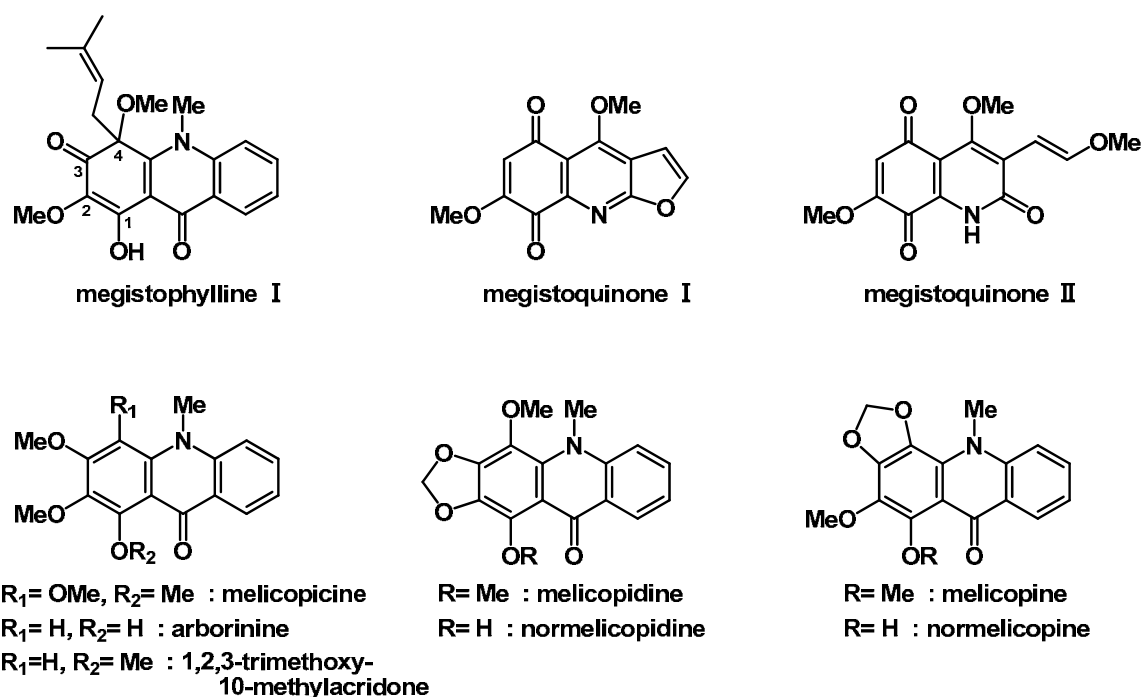


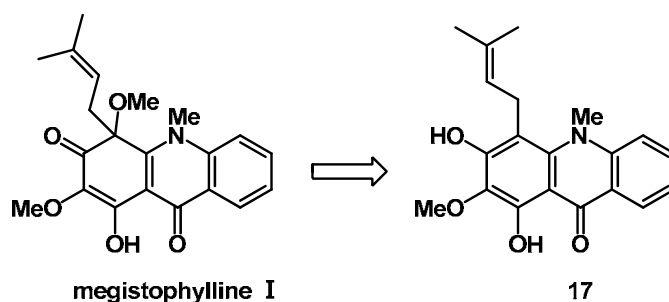
Figure 13

Megistophylline は著者らが γ -mangostinを陽極酸化反応に付した際に得られた化合物と類似した骨格を有していることから、この天然物にもグラム陽性菌および陰性菌に対する抗菌活性やMRSAに対するイミペネムの抗菌活性増強作用などその生物活性が期待されるため、合成研究に着手した。

2. ベンゾフェノン誘導体を中間体とした合成

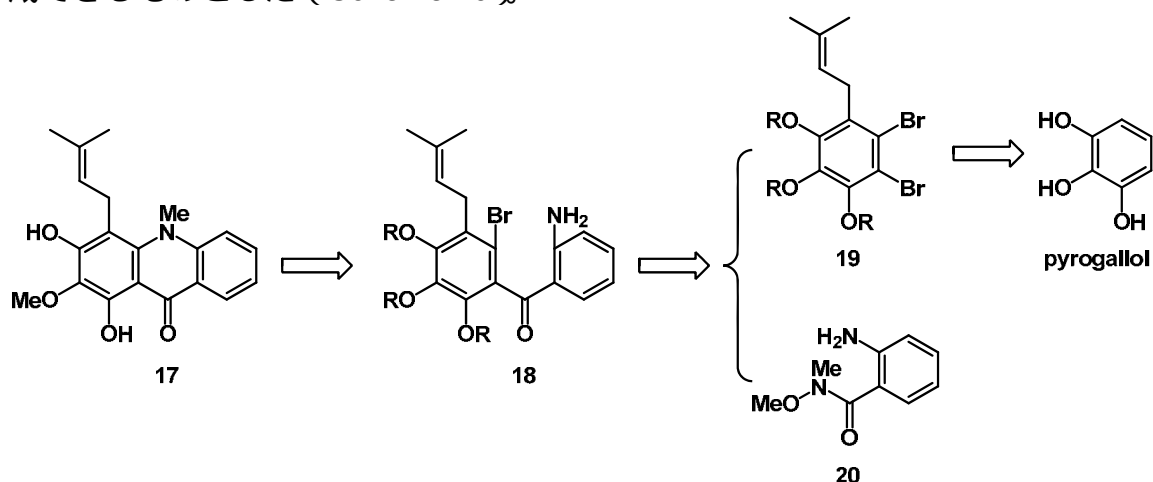
2 - 1 . 逆合成解析

Megistophylline を合成するにあたり、標的構造であるジエノン骨格はアクリドン骨格を構築したのち、化合物 **17** を γ -mangostin から誘導した手法と同様に陽極酸化反応を活用することでの合成を期待した (Scheme 9)。



Scheme 9

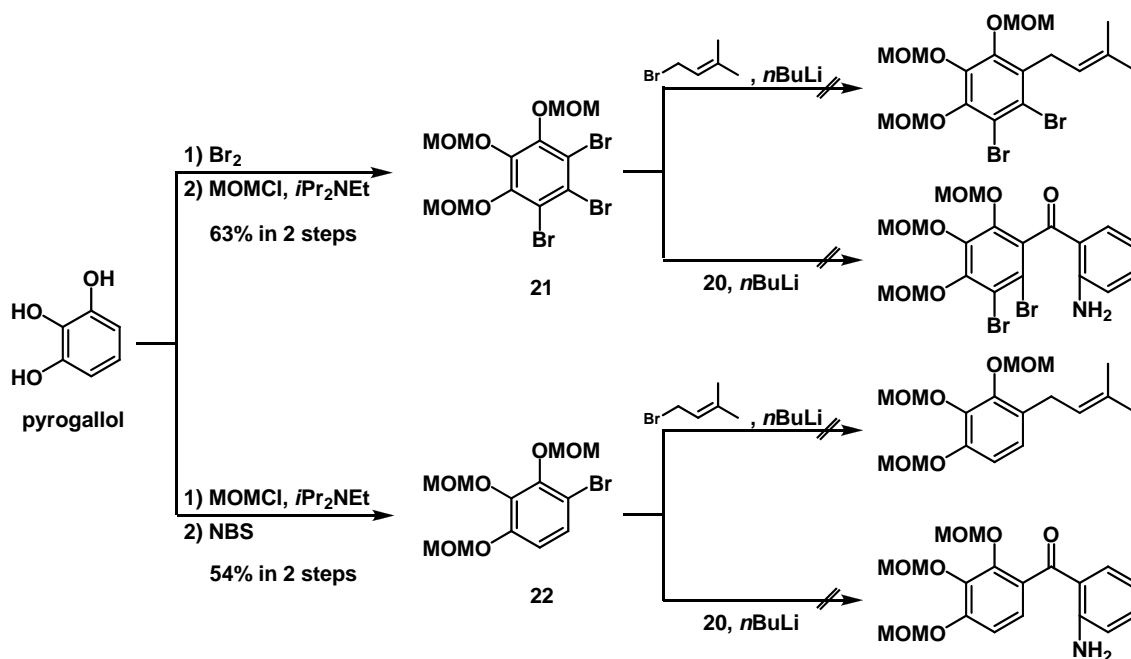
酸化前駆体となる化合物 **17** を合成するにあたり、その前駆体となるアクリドン骨格 **18** はベンゾフェノン誘導体を環化反応に付すことにより合成できるものとした。ベンゾフェノン誘導体は化合物 **19** と **20**³¹⁾ のカップリングにより合成できるものとし、また化合物 **19** は pyrogallol を出発物質として用いることで合成できるものとした (Scheme 10)。



Scheme 10

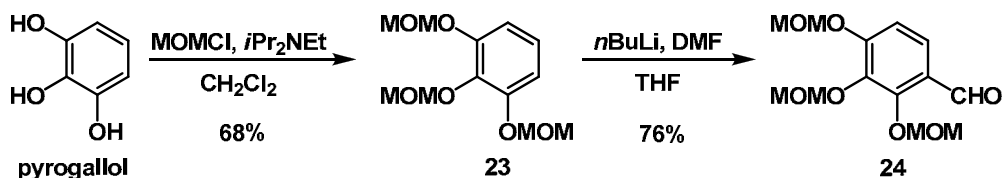
2 - 2 . ベンゾフェノン中間体を経るアクリドン骨格の構築

前述の方法に従い、pyrogallol をトリプロモ化し³²⁾、ついでフェノールを MOM 基で保護することにより化合物 **21** へと導いた (Scheme 11)。この化合物 **21** にリチオ化を経てプレニル基の導入を試みたが、反応は進行しなかった。そこで、先に化合物 **20** とのカップリングを試みたが同様に反応は進行しなかった。また、トリプロモ体の代替としてモノプロモ体 **22** を用いて同様にプレニル基の導入、カップリング反応を試みたが、この場合においても成功しなかった。



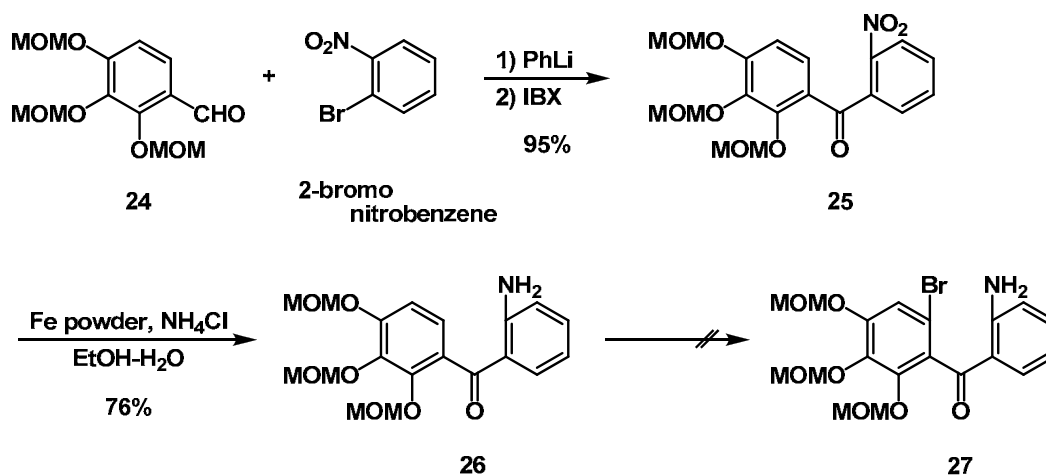
Scheme 11

そこで、カップリングした後にハロゲン化を行い、環化反応に付すことでアクリドン骨格の構築が出来るのではないかと考えた。先と同様に pyrogallol を出発物質として合成した MOM 体 **23** に対し *n*BuLi を作用させることでオルトリチオ化し、その後 DMF を加えてホルミル化することで³³⁾、アルデヒド体 **24** を得た (Scheme 12)。



Scheme 12

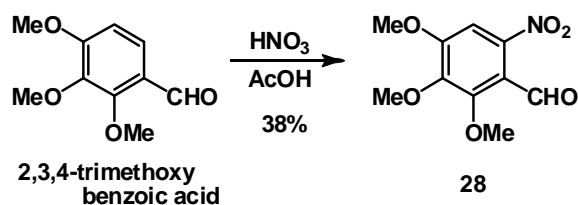
得られたアルデヒド体 **24** と 2-bromonitrobenzene とカップリング、続く IBX³⁴⁾ 酸化反応を行うことでベンゾフェノン体 **25** へと誘導した (Scheme 13)。化合物 **25** に対し酸性条件下、鉄粉を用いて還元し、アミン体 **26** へとした後、環化の際に脱離基となる Br 基の導入を試みたが、目的物 **27** を得ることは出来なかった。



Scheme 13

続いて、アルデヒドおよびニトロ基を左側のセグメントに導入し、右側のセグメントにリチオ化の足掛かりとなる Br 基および脱離基を導入した化合物を設定することでカップリング反応、続く環化反応が可能であると考えた。

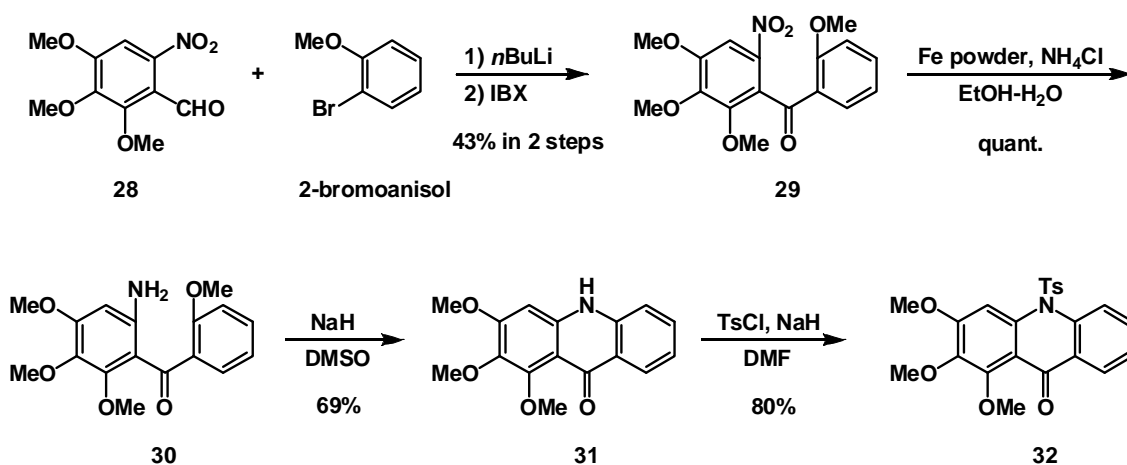
始めに、2,3,4-trimethoxybenzaldehyde をニトロ化し³⁵⁾、化合物 **28** とした (Scheme 14)。



Scheme 14

この化合物 **28** と 2-bromoanisole を *n*BuLi を用いてカップリング、続く IBX 酸化でベンゾフェノン誘導体 **29** を合成した (Scheme 15)。化合物 **29** を酸性条件下、鉄粉を用いて還元してアミン体 **30** とした後、環化反応を行いアクリドン体 **31** を得た。この化合物 **31** のアミン部位が天然物と同様の N-Me 体の場合、陽極酸化反応時にフェノールではなくアミン部位が酸化される恐れがあったため、電子吸引性基である Ts 基を用いることとした。化合物 **31** に対し DMF 中水素化ナトリウム、TsCl を用いて反応を行ったところ 80% の収率で化合物 **32** を

得た。しかしながら、化合物 **32** に対し O-Me 基のフェノール体への変換を種々検討したが、目的物を得るに至らなかった。



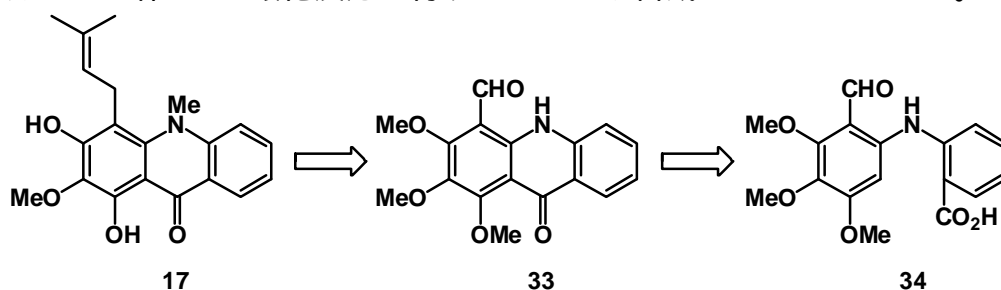
Scheme 15

化合物 **32** からの脱保護は困難であったため、環化前およびカップリング前に保護基の変換を種々試みたが、メチル基の脱保護をニトロ基導入前に行った場合、種々検討したがニトロ基が導入できず、カップリング前駆体へと誘導することができなかった。

3. ジアリールアミン体を中間体とした合成

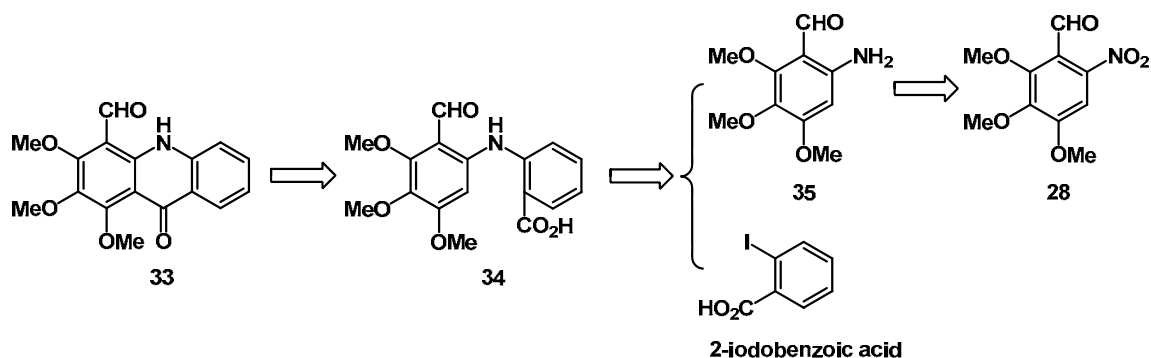
3 - 1 . 逆合成解析

続いて、ジアリールアミン体の環化反応を用いるアクリドン骨格の構築を行うルートについて検討を行うこととした (Scheme 16)。すなわち酸化前駆体 **17** はアクリドン体 **33** から誘導できるものとした。また、アクリドン体 **33** はジアリールアミン体 **34** を環化反応に付すことにより合成できるものとした。



Scheme 16

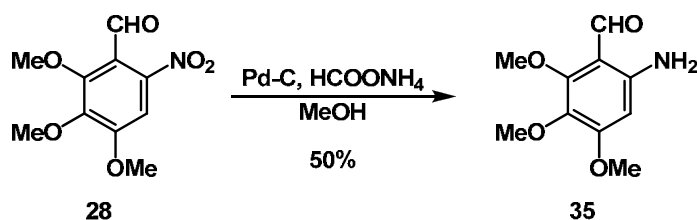
アクリドン体 **33** の前駆体であるジアリールアミン体 **34** はアミン体 **35** と 2-iodobenzoic acid の Ullmann 反応によるカップリングにより合成できるものとし、アミン体 **35** は先に合成したニトロ体 **28** を還元することにより得られるものとした (Scheme 17) また、先述で問題となった Me 基の位置選択的脱保護は、環化反応の後、1 位はケトン基との水素結合、3 位は 4 位のホルミル基との水素結合を利用することにより可能であると考えた。



Scheme 17

3 - 2 . 酸化反応を鍵反応とした合成

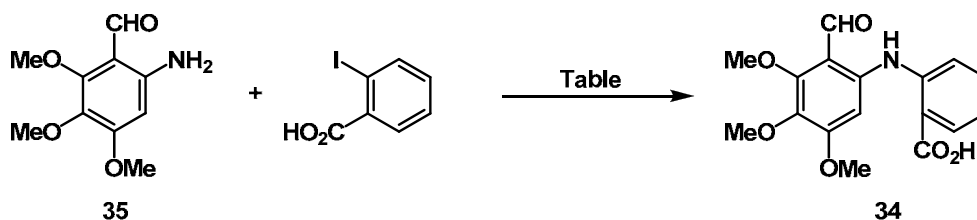
ニトロ体 **28** を 10% Pd-C、ギ酸アンモニウムの条件で還元し、アミン体 **35** とした (Scheme 18)。合成されたアミン体 **35** と 2-iodobenzoic acid の Ullmann 反応を用いたジアリールアミン体 **34** の構築に向けた検討を行うこととした。



Scheme 18

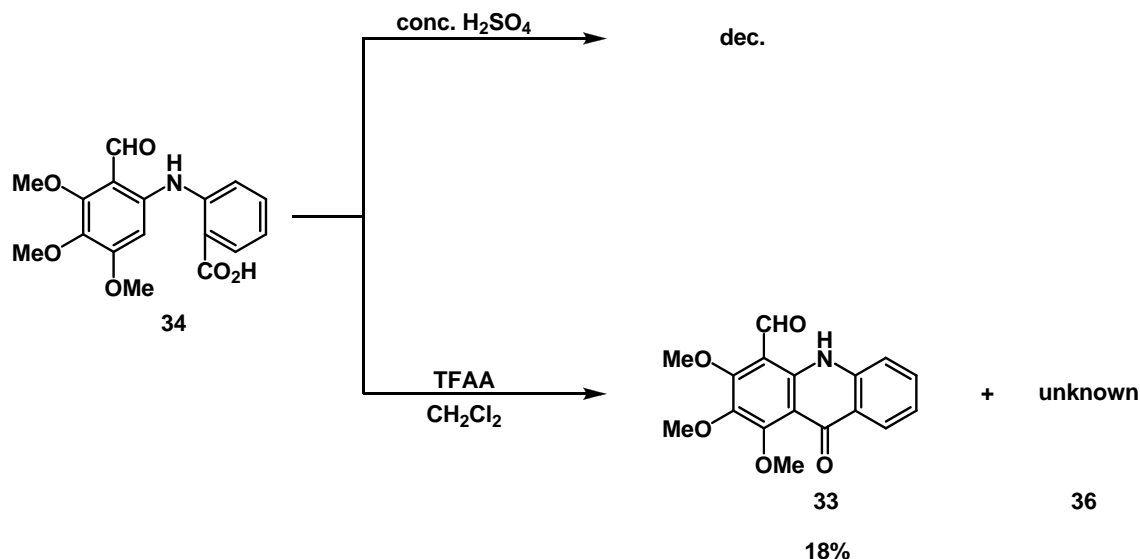
Table 3 に示した条件で Ullmann 反応の検討を行った³⁶⁾。その結果、entry 3 に示した条件では目的物 **34** を得ることはできなかったが、entry 1 および 2 共に低収率であったが目的のジアリールアミン体を得ることができたため、先の検討を行うこととした。

Table 3 Ullmann 反応の検討



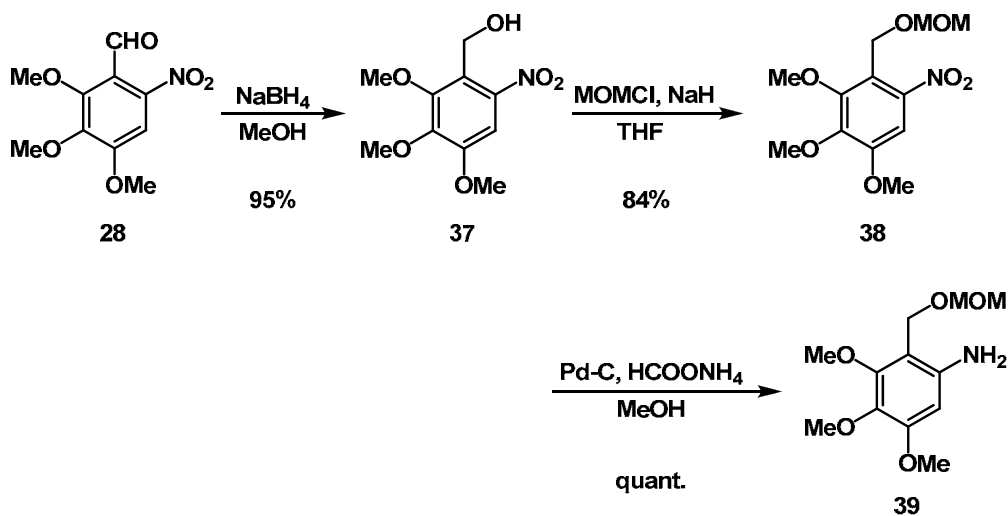
entry	conditions	result (%)
1	CuI, K ₂ CO ₃ , DMF 100 °C	20
2	CuCl, K ₂ CO ₃ , 2-propanol reflux	32
3	Cu, K ₂ CO ₃ , 2-propanol reflux	dec.

得られたジアリールアミン体 **34** に対し、環化反応を試みた。すなわち、濃硫酸条件³⁷⁾で反応を行った場合、環化体の生成は認められず、複雑な反応系となったのに対し、TFAA を用いたところ³⁸⁾、低収率ではあるがアクリドン体 **33** を得ることに成功した(Scheme 19)。しかしながら、アルデヒド部位で環化したような化合物 **36** がより多く得られてきたことから、アルデヒドをアルコールへと還元した後に環化反応を試みることにした。



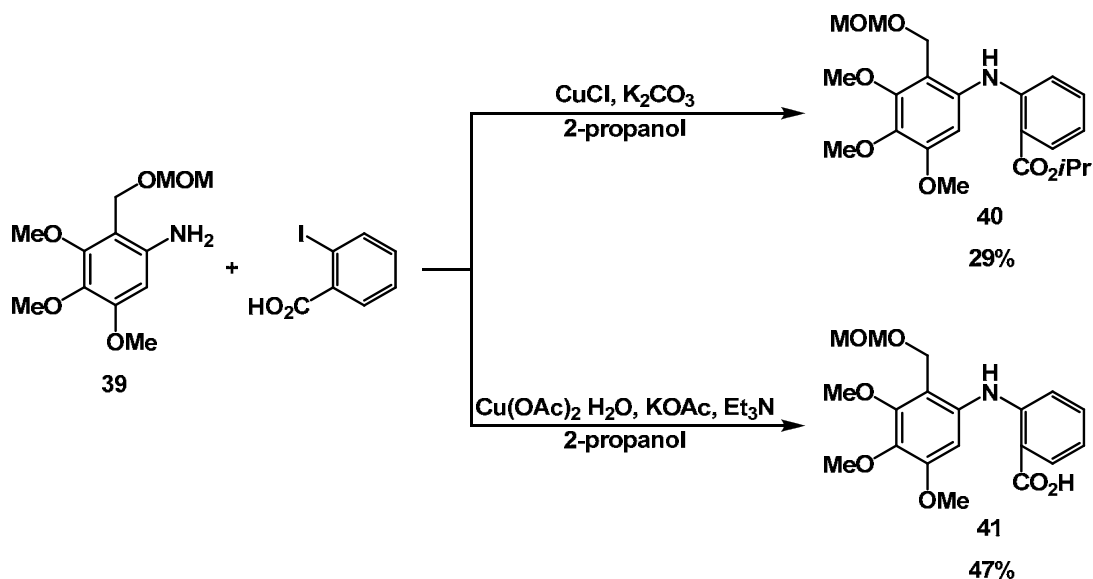
Scheme 19

アルデヒド体 **28** を NaBH₄ を用いて還元しアルコール体 **37** とした。化合物 **37** の水酸基を MOM 基により保護し、化合物 **38** とした後、ニトロ基を還元してアミン体 **39** を合成した(Scheme 20)。



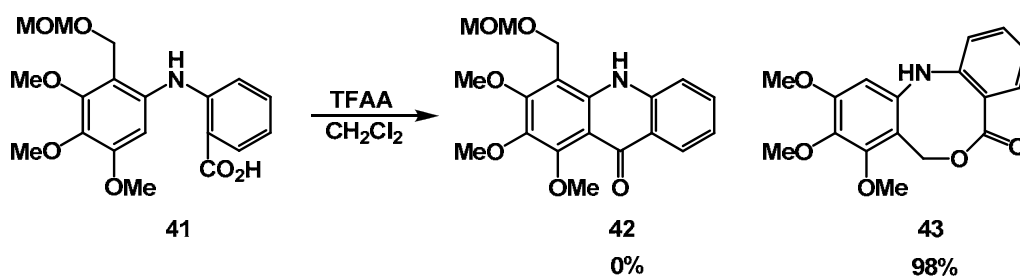
Scheme 20

続いて Ullmann 反応を行うこととした (Scheme 21)。化合物 **34** 合成時と同様の条件で反応を試みたところ、溶媒である 2-propanol が縮合したエステル体 **40** のみが得られた。そこで、銅試薬を塩化銅 () から酢酸銅 () 一水和物³⁸⁾へと変更したところ、目的のジアリールアミン体 **41** が得られた。



Scheme 21

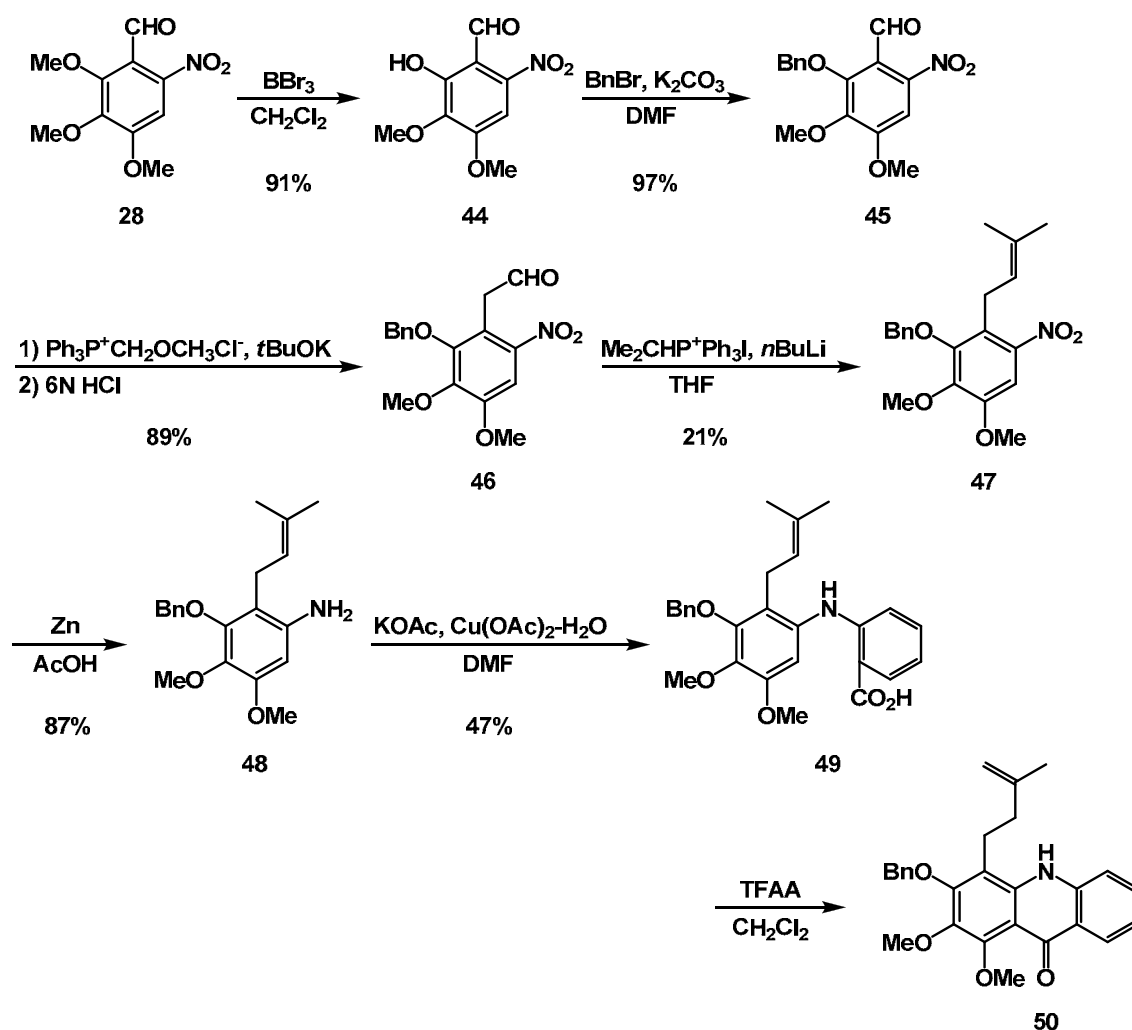
化合物 **41** を TFAA を用いた環化反応に付したところ、目的のアクリドン体 **42** を得ることは出来ず、定量的にベンジル位で環化が進行した化合物 **43** が得られた (Scheme 22)。



Scheme 22

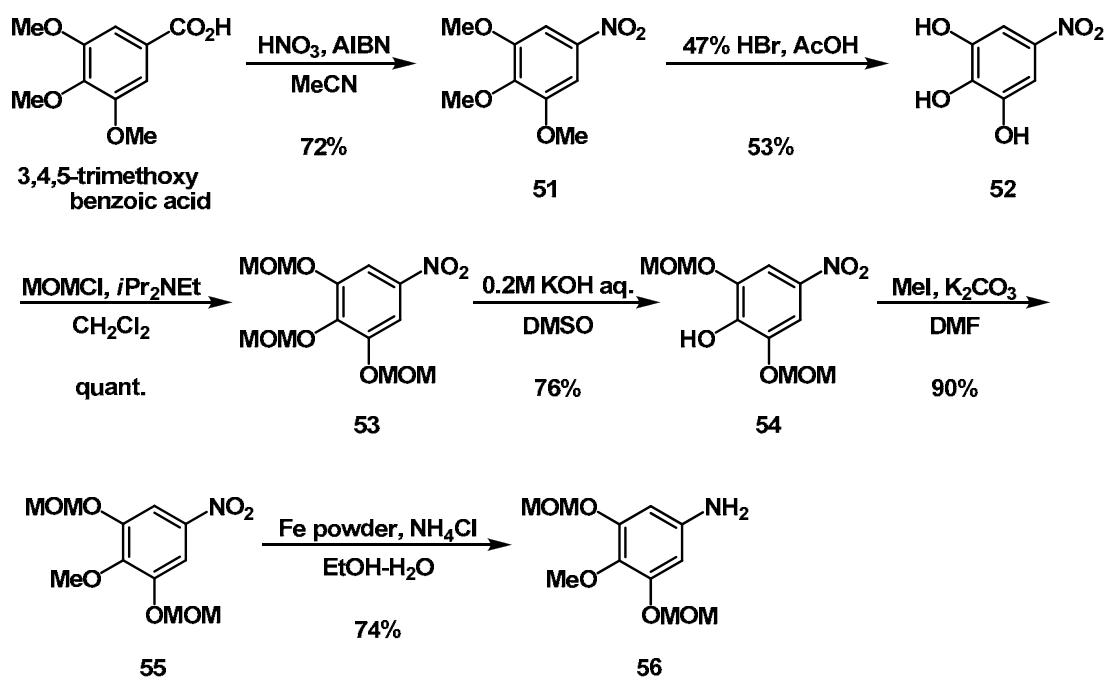
アルコール体では 1 級の酸素官能基が脱離してしまうことが判明したため、アルデヒドをアセタール保護した化合物を用いて検討を行うことを考えたが、ニトロ基の還元時に脱保護されたため、プレニル基を先に構築した後、環化反応を試みることにした。

先にニトロ **28** のアルデヒド基のオルト位の Me 基を除去し化合物 **44** とした後、フェノールを Bn 基で保護した化合物 **45** へと誘導、続く Wittig 反応、酸加水分解に付すことで一炭素増炭した化合物 **46** とした(Scheme 23)。化合物 **46** に対しさらに Wittig 反応を行うことでプレニル基を構築して化合物 **47** とした後、ニトロ基を亜鉛還元で付すことでアミン体 **48** へと変換し、得られたアミン体 **48** を Ullmann 反応に付すことで環化前駆体であるジアリールアミン体 **49** の合成を達成した。この化合物 **49** に対して環化反応を試みたところ、環化反応は進行したものの、プレニル基の異性化を伴った化合物 **50** が得られた。末端オレフィンから内部オレフィンへの異性化を種々試みたが、望む反応は進行しなかったため環化以前にプレニル基を導入する経路ではなく、4 位への置換基の導入は環化後に行うことにした。



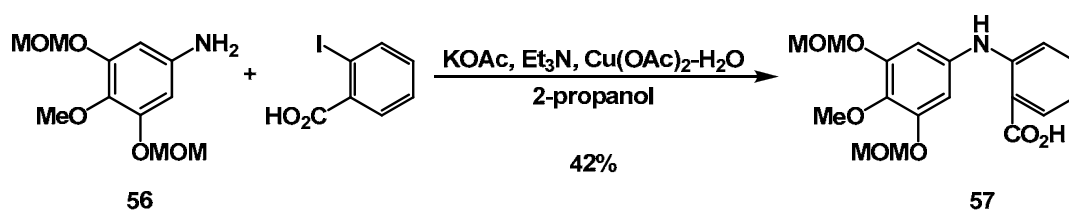
Scheme 23

3,4,5-Trimethoxybenzoic acid をニトロ化して化合物 **51**³⁹⁾とした後、酸性条件下でメチル基を脱保護⁴⁰⁾して化合物 **52**を得た(Scheme 24)。フェノールを MOM 基で保護して化合物 **53** へとした後、4 位のみフェノールとし⁴¹⁾化合物 **54** とした。この化合物 **54** のフェノールをメチル基で保護し、ニトロ基を酸性条件下において鉄粉を用いた還元反応を行うことで、Ullmann 反応の前駆体となるアミン体 **56** へと誘導した。



Scheme 24

得られたアミン体 **56** と 2-iodobenzoic acid を Ullmann 反応に付したところ、収率は 42%と中程度ではあったが、目的のジアリールアミン体 **57** を得ることが出来た(Scheme 25)。しかしながら、化合物 **57** からの環化反応は、系中が複雑な混合物となり、目的の環化体の生成は認められなかった。酸性による MOM 基の脱保護が系中を複雑化させる要因の一つと考えられたため、あらかじめ MOM 基を脱保護した化合物からの環化も試みたが、望みの環化体を得ることは出来なかった。

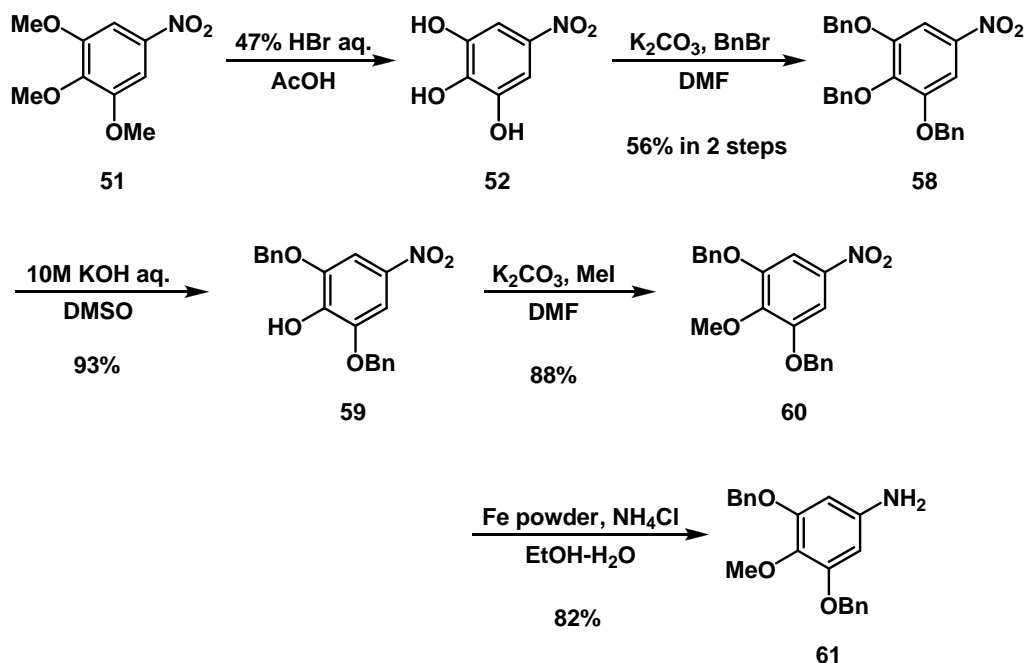


Scheme 25

そこで、MOM 基から TFAA 中で耐え得る保護基である Bn 基へと変換して同様の反応を試みることにした。

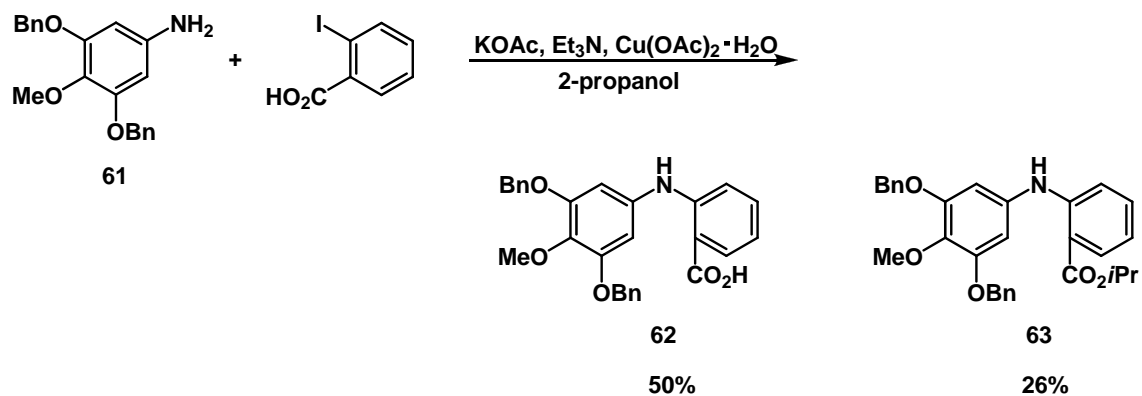
すなわち、先と同様にニトロ体 **51** のメチル基を除去し、粗精製の状態で Bn 基により保護することで化合物 **58** を得た(Scheme 26)。4 位の BnO 基のみを塩基性条件下選択的にフェノールへと変換し、Me 基で保護することで化合物 **60** とした。この化合物 **60** に対し、鉄粉を用いてニトロ基の還元を行い、Ullmann 反

応前駆体となるアミン体 **61** を合成した。



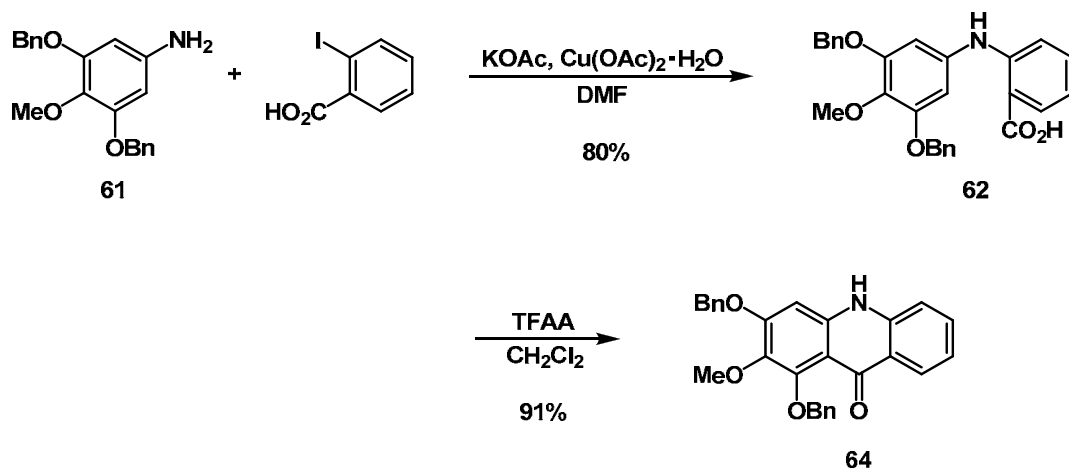
Scheme 26

続いて先と同様の条件で Ullmann 反応を行った。その結果、目的とするジアリールアミン体 **62** の他に、溶媒として用いていた 2-propanol が導入された化合物 **63** も同時に得られた(Scheme 27)。

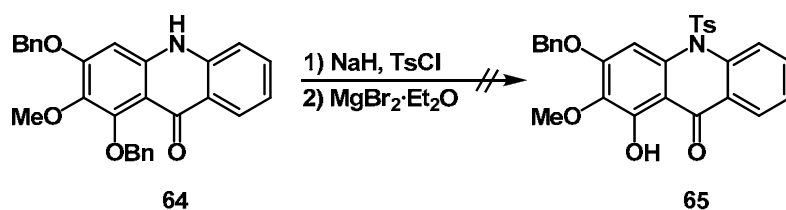


Scheme 27

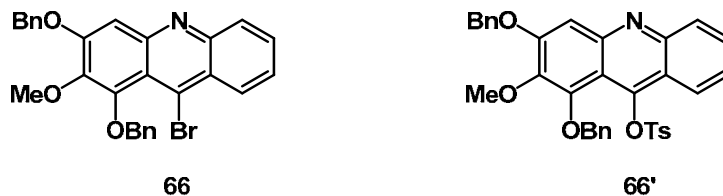
そこで、溶媒を 2-propanol から DMF へと変更して Ullmann 反応を行ったところ目的とするジアリールアミン体 **62** のみを 80%の収率で得ることが出来た(Scheme 28)。このジアリールアミン体 **62** に対し TFAA を用いて環化反応を行ったところ、アクリドン誘導体 **64** の合成を達成した。



アクリドン体 **64** に対し、先と同様に DMF 中 TsCl、NaH を作用させ Ts 基の導入を行った後、選択的な Bn 基の脱保護を狙い、MgBr₂·Et₂O を作用させた⁴²⁾ところ、目的の脱 Bn 体 **65** を得ることはできなかった (Scheme 29)。

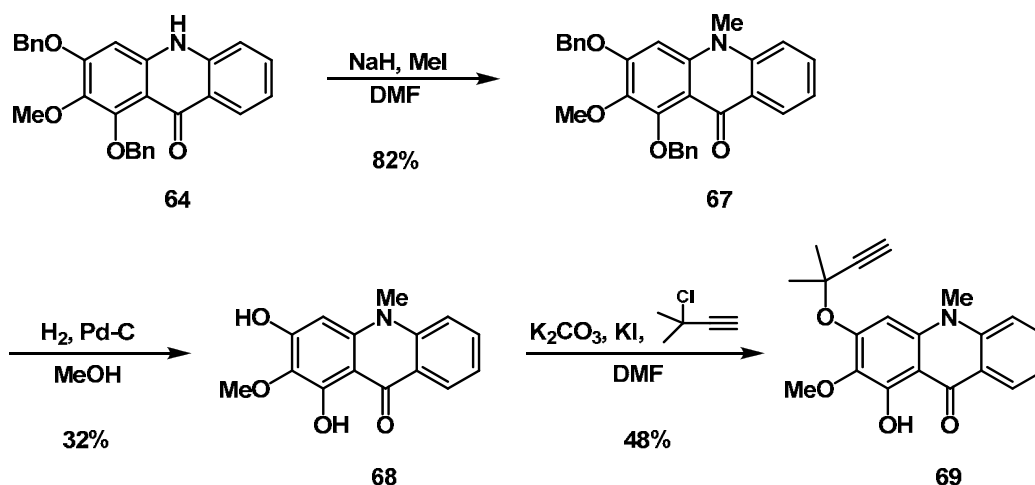


得られた化合物の構造は 1H NMR スペクトルおよび MS スペクトルより Figure 14 に示した化合物 **66** であること判明した⁴³⁾。このことから Scheme 29 に示した反応条件において、一段階目の反応での生成物は N-Ts 体ではなく C-9 位のケトン部位が O-Ts 化された化合物 **66'** であることが示唆された。



Ts 基以外の吸引性基によるアミノ部位の保護を試みたが、反応が進行しない、または化合物 **66'** と同様の化合物が得られたため、陽極酸化反応時に酸化してしまう恐れはあるものの、N-Me 体とすることとした。

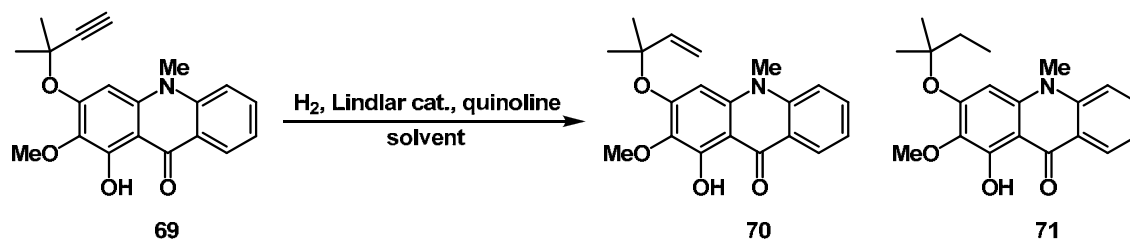
アクリドン体 **64** のアミノ基を Me 化して化合物 **67** とし、加水素分解反応を行うことで化合物 **68** とした。この化合物 **68** に 3-chloro-3-methyl-1-butyne を作用させ⁴⁴⁾、プロパルギル体 **69** とした (Scheme 30)。



Scheme 30

プロパルギル体 **69** に対して Lindlar 触媒⁴⁵⁾を用いたオレフィンへの還元を試みた。その結果 Table 4 に示した 3 種の溶媒ではいずれの溶媒を用いても目的物 **70** は得られるが、同時に過剰に還元が進行した化合物 **71** の生成も認められた。

Table 4 Lindlar 触媒を用いたプロパルギル基の還元についての検討

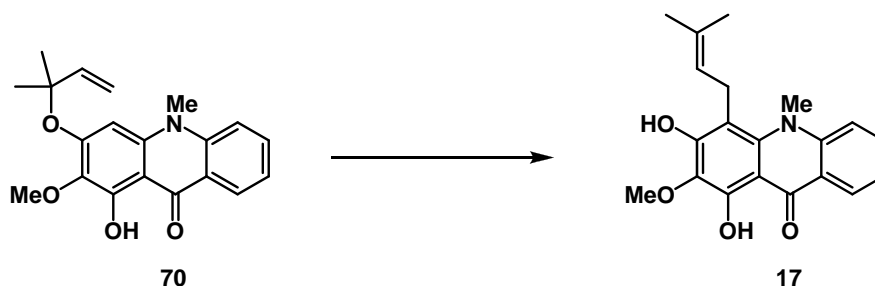


entry	solvent	result (%)	
		70	71
1	MeOH	24	55
2	EtOAc	22	39
3	benzene	27	53

得られた化合物 **70** を用いて Claisen 転位の検討を行った。いずれの条件においても目的物を得ることが出来ず、また entry 4 に示した条件では 4 位ではなく 2 位に転位したような化合物が得られた。しかしながらこの化合物は予想外に不

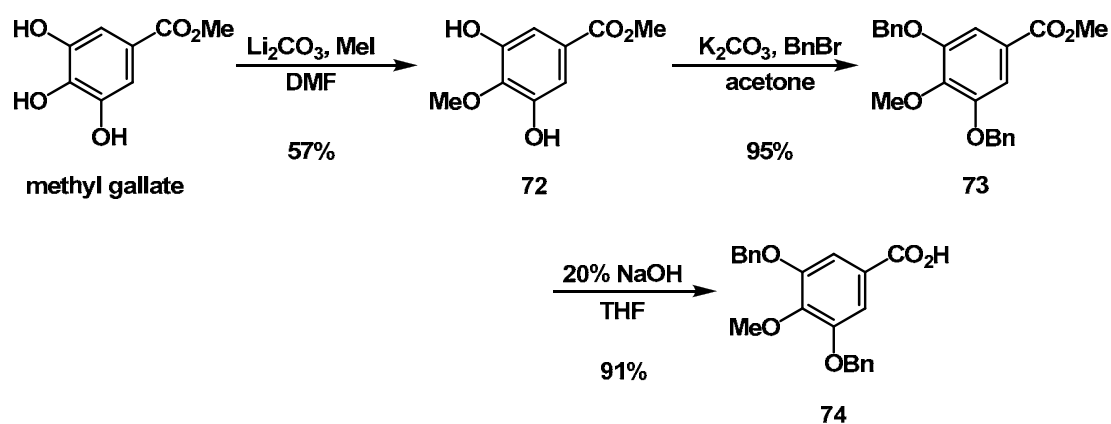
安定であったため、構造決定には至らなかった。

Table 5 Claisen 転位の検討



entry	solvent	temp. (°C)	result
1	DMF	130	dec.
2	toluene	100	n.r.
3	xylene	130	n.r.
4	xylene	140	unknown

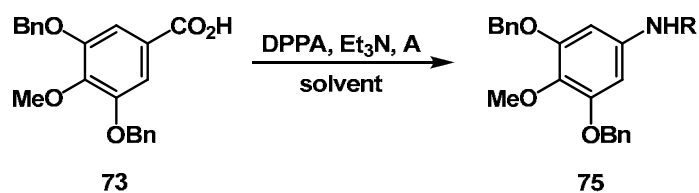
そこで、Claisen 転位を 3 位からではなく 1 位から行うことでもプレニル基の導入が行えるのではないかと考えた。先と同様の方法では Me 基の脱保護の際、反応の再現性をとること、および精製が極めて困難であったことから合成ルートを変更することとした。すなわち methyl gallate を出発物質とし、4 位のフェノールを選択的に Me 基で保護して化合物 **72**⁴⁶⁾ とした (Scheme 31)。2 つのフェノールを Bn 基で保護し化合物 **73** とし、メチルエステルを加水分解してカルボン酸 **74** とした後 Curtius 転位反応を行い、アミン体へと変換することとした。



Scheme 31

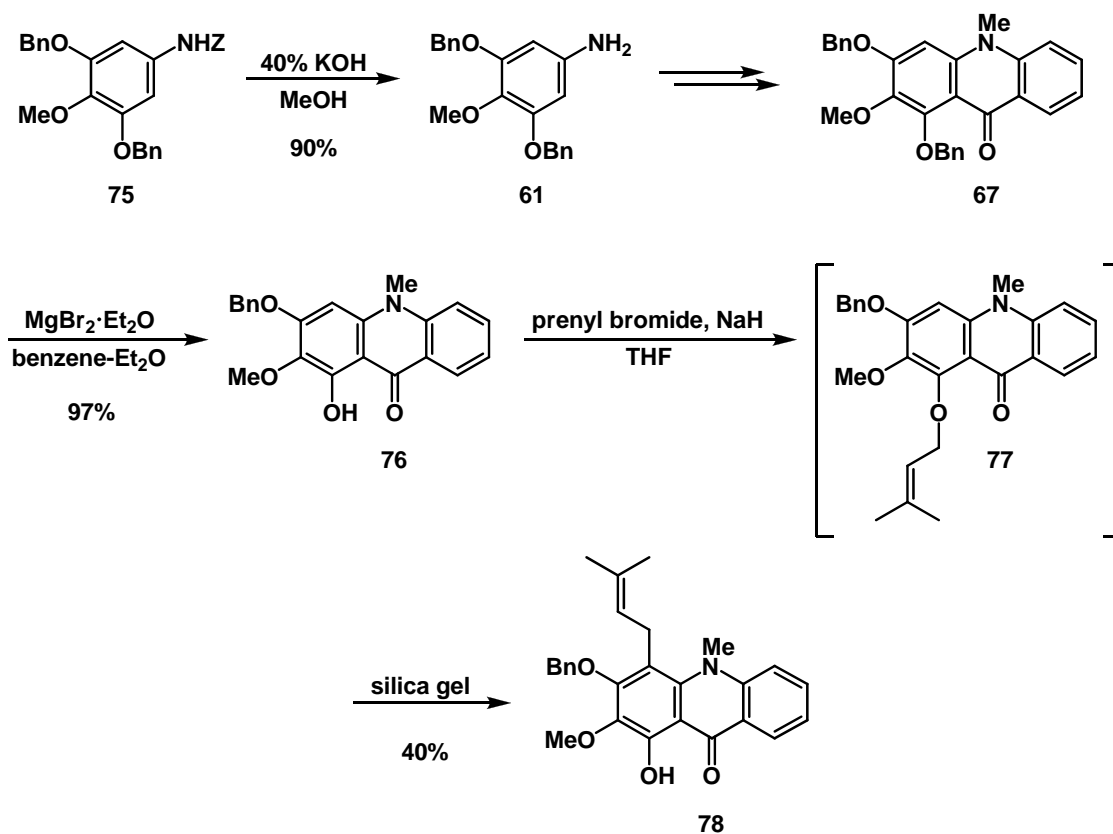
そこで、Crutius 転位⁴⁷⁾の検討を行った (Table 6)。最初に、entry 1 に示した条件で直接アミン体への変換を試みた。その結果目的物は得られたが、その収率はかなり低いものとなった。また、水のかわりに *t*BuOH を用いたところ、entry 1 の時と同程度の収率となった。両者に共通する要因としては *t*BuOH にも水が多く含まれていたことから、反応中間体が水に不安定であることが示唆された。そこで entry 3 に示したように BnOH を用いて反応を行ったところ、定量的に反応は進行し、Z 基で保護されたアミン体 **75** を得た。

Table 6 Crutius 転位の検討



entry	A	solvent	R	result (%)
1	H ₂ O	THF	H	18
2	<i>t</i> BuOH	toluene	Boc	17
3	BnOH	toluene	Z	quant.

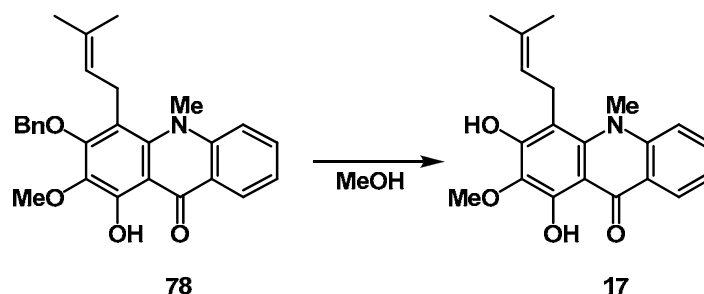
化合物 **75** の Z 基を脱保護し、得られたアミン体 **61** に対して先ほどと同様に 2-iodobenzoic acid と Ullmann 反応に付し、環化反応、続く Me 化によりアクリドン体 **67** とした後、1 位の Bn 基のみを脱保護し化合物 **76** を得た (Scheme 32)。この化合物 **76** に対し prenyl bromide を用いて 1 位にプレニル基を導入したところ、反応系中で化合物 **77** の他に一部 Claisen 転位の進行した化合物 **78** の生成が TLC 上で確認された。また、精製時にシリカゲル上でも転位が進行することが判明したため、シリカゲルに展着した後一夜放置したのち溶離することにより、加熱することなく芳香環上にプレニル基の導入された化合物 **78** を得ることに成功した。



Scheme 32

化合物 **78** の Bn 基の脱保護を試みた (Table 7)。当初、entry 1 に示したように 10% Pd-C を用いて脱保護を試みたが、触媒に基質が吸着されることにより回収不能となった。そこで他の Pd 触媒を用いて反応を試みたところ、entry 2 に示した Pd/BaSO₄ の条件下では反応は全く進行せず、entry 3 に示した Pd black を用いた場合に Bn 基の脱保護が進行し、酸化前駆体となる化合物 **17** を得ることができた。

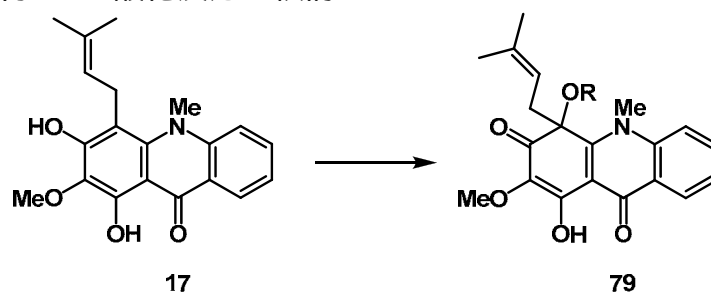
Table 7 Bn 基の脱保護の検討



entry	conditions	result (%)
1	10% Pd-C, cyclohexene	0
2	Pd/BaSO ₄ , 1,4-cyclohexadiene	n.r.
3	Pd black, 1,4-cyclohexadiene	71%

化合物 17 に対して種々の酸化反応を試みた (Table 8)。まず、entry 1 に示す γ -mangostin を酸化し、化合物 5 を合成した時と同条件による酸化反応を試みたところ、目的物ではない構造不明物を得た。また、entry 2 に示した PIFA や entry 3 に示した iodobenzene の陽極酸化反応による酸化成績体のような超原子価ヨウ素を用いて酸化反応を行った場合においても entry 1 と同様の構造不明物が得られ、目的物を得ることはできなかった。続いて金属酸化試薬による酸化反応を試みたところ、entry 4 および 5 に示した条件では反応は進行しなかったが、Pb(OAc)₄ を酸化剤として用いたところ 3 位が酸化され 4 位に AcO 基の導入された目的の構造を有する化合物 79 が得られた。

Table 8 化合物 17 の酸化反応の検討



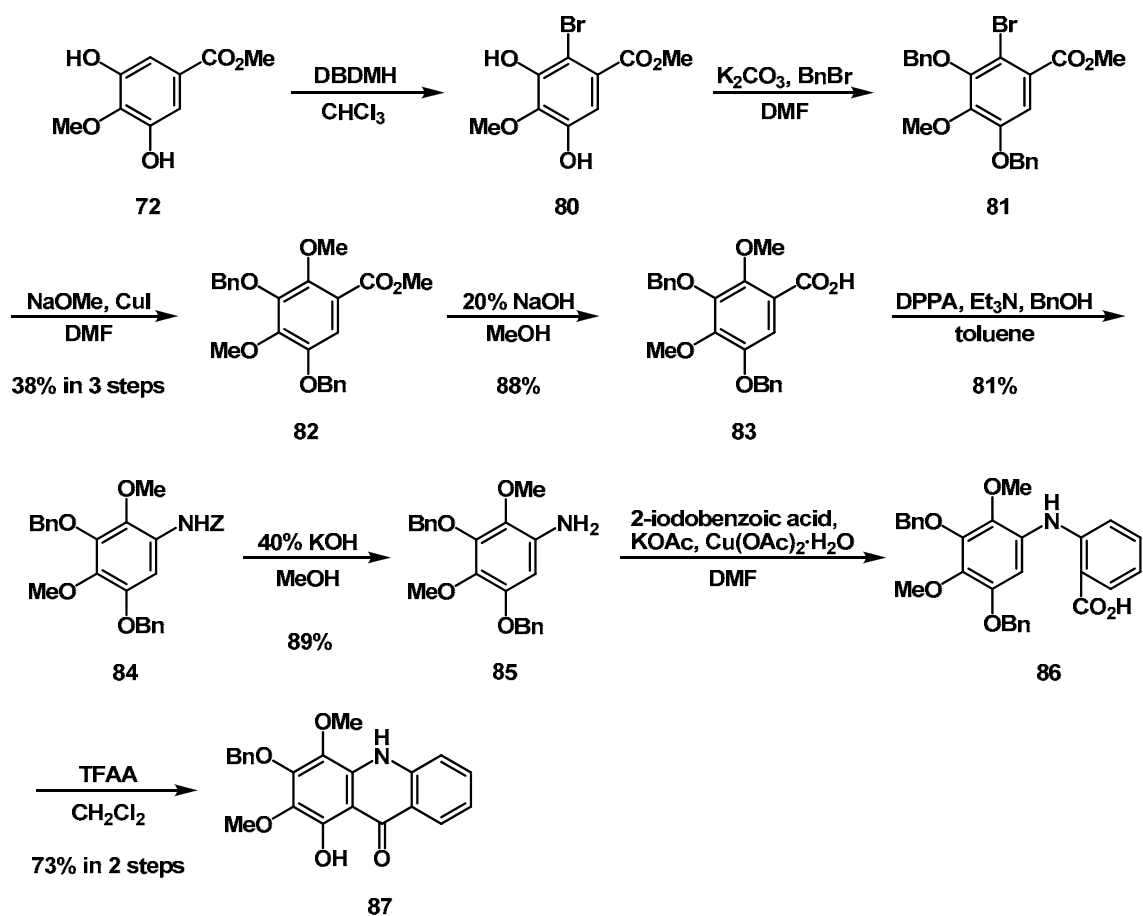
entry	R	conditions	result (%)
1	Me	C.C.E. (0.3 mA/ cm ²), 2F/ mol, MeOH	unknown
2	Me	PIFA, MeOH	unknown
3	Me	Ph(OCH ₂ CF ₃), MeOH	unknown
4	Me	FeCl ₃ , MeOH	n.r.
5	Me	PbO ₂ , MeOH	n.r.
6	Ac	Pb(OAc) ₄ , benzene	72%

化合物 79 の Ac 基の脱保護を種々検討したが、この化合物自体の不安定性のため、Ac 基の除去が進行する以前に骨格自体が反応に耐えられず、目的物を得ることは出来なかった。

そこで、3 位、4 位の骨格構築を酸化ではなく、あらかじめ 4 位に MeO 基を導入した化合物に対して Claisen 転位反応を行い、プレニル基を導入することで骨格構築を試みることにした。

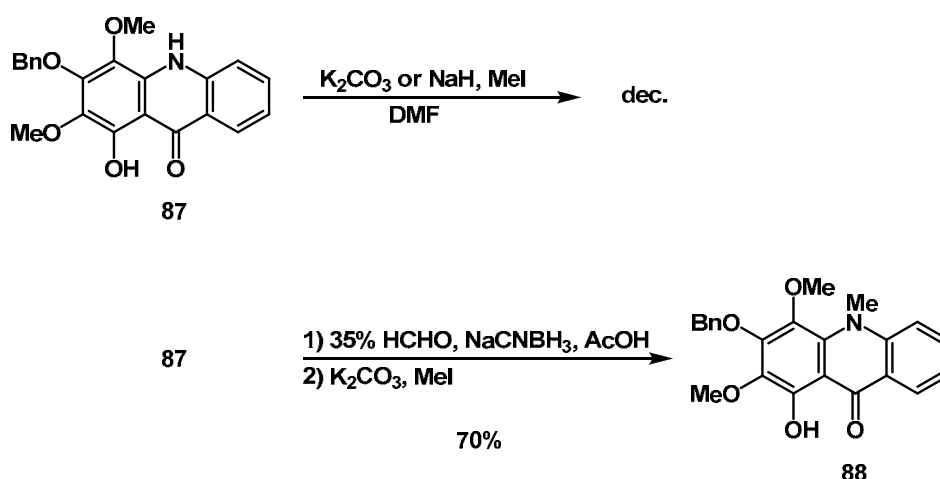
3 - 3 . Claisen 転位反応を鍵反応とした合成

まず、先に合成した化合物 72 に対し DBDMH を用いてプロモ化⁴⁸⁾を行った (Scheme 33)。原料およびモノプロモ体、ジプロモ体の分離は困難であったため、混合物の状態での Bn 化、続く MeO 基の導入⁴⁹⁾を行うことで化合物 82 を得た。先と同様に化合物 82 のメチルエステルを加水分解によりカルボン酸 83 へと変換し、Crutius 転位反応により Z 基で保護されたアミン体 84 へと誘導した。この化合物 84 の Z 基を脱保護してアミン体 85 とした後 Ullmann 反応に付すことでジアリールアミン体 86 を合成した。さらに、環化反応に付すことでアクリドン誘導体 87 へ誘導した。



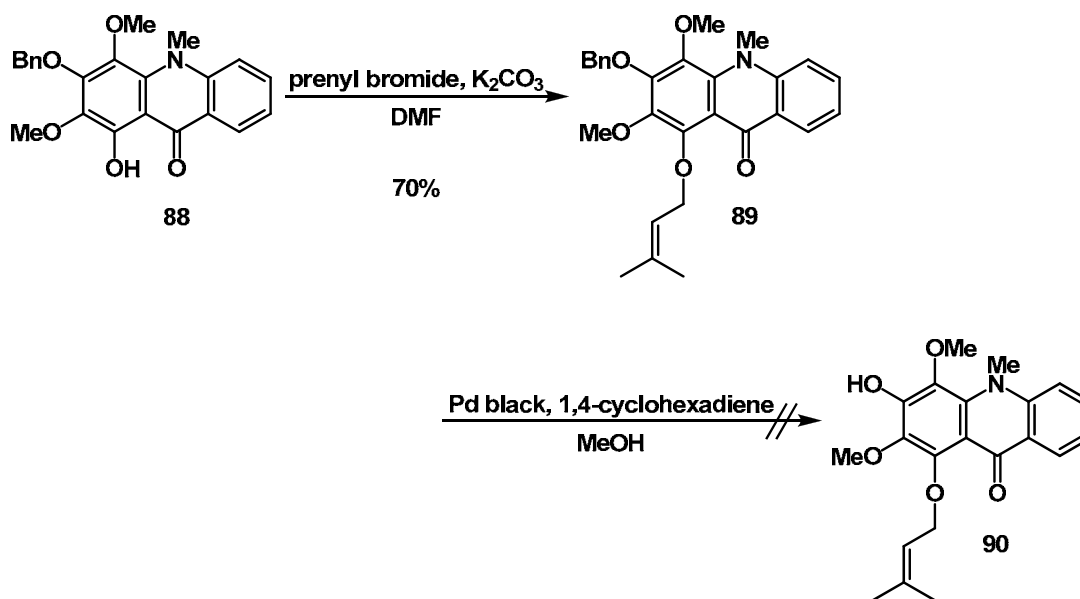
Scheme 33

この化合物 **87** のアミノ基に Me 基の導入を試みたところ、塩基とヨウ化メチルの条件では基質の分解が進行し、目的物が得られないことが判明した (Scheme 34)。そこで還元的 Me 化法により化合物を合成することとした。その結果、N-Me 化は進行したもののフェノールの Me 基が一つ脱離したため、再度得られた化合物に対し Me 化を行い、化合物 **88** へと誘導した。



Scheme 34

次に、1 位にプレニル基を導入した化合物からの Claisen 転位を試みることにした。化合物 **88** の 1 位に prenyl bromide、炭酸カリウムの条件にてプレニル基を導入して化合物 **89** とした(Scheme 35)。続いて Bn 基の脱保護を試みたが、Bn 基の脱保護と同時にプレニル基の脱離も進行したため、3 位のフェノールが脱保護された Claisen 前駆体 **90** の合成には至らなかった。

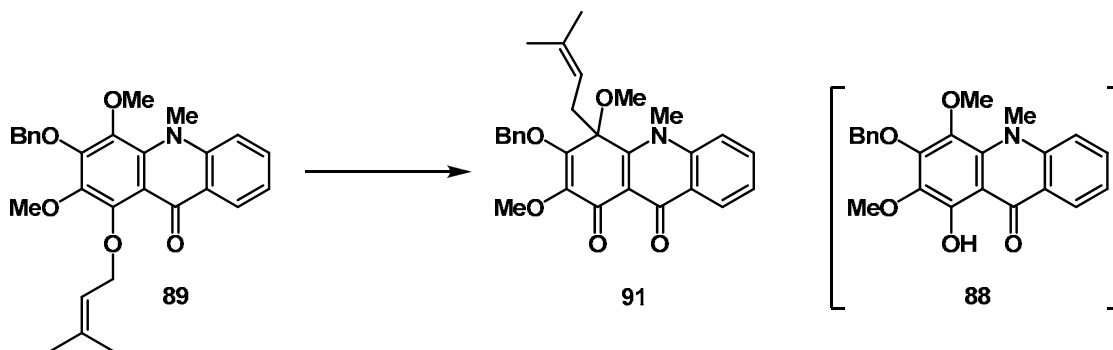


Scheme 35

そこで脱保護を Claisen 転位反応後に行うこととし、最初に化合物 **89** からの Claisen 転位を試みた(Table 9)。その結果、xylene を用いた entry 1、2 の条件では反応はほとんど進行せず、高温条件下、長時間の反応では基質の分解が進行することが判明した。また、entry 3~5 に示した条件では速やかにプレニル基の

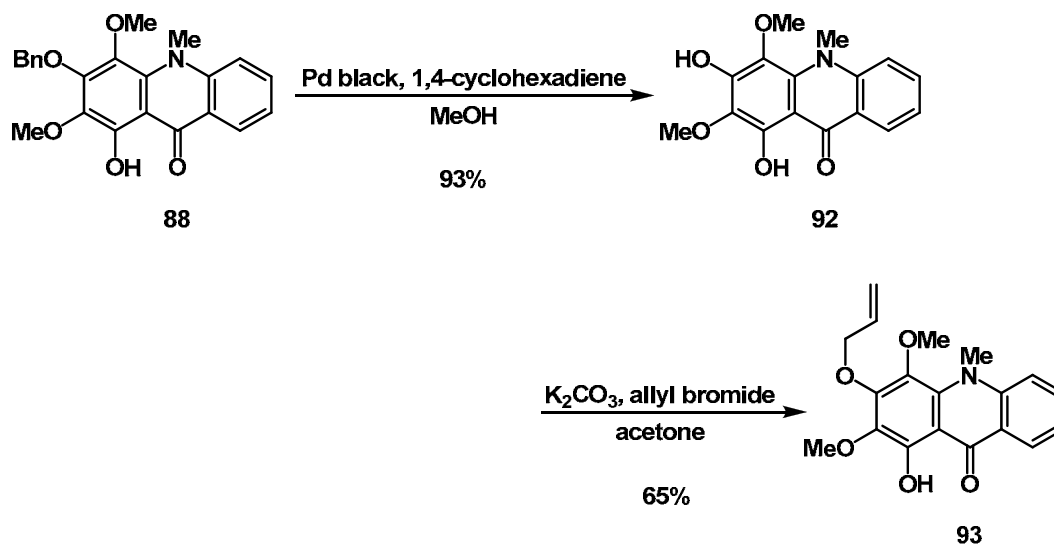
脱離が起こり、Claisen 転位した化合物 **91** を得ることはできなかった。

Table 9 Claisen 転位の検討



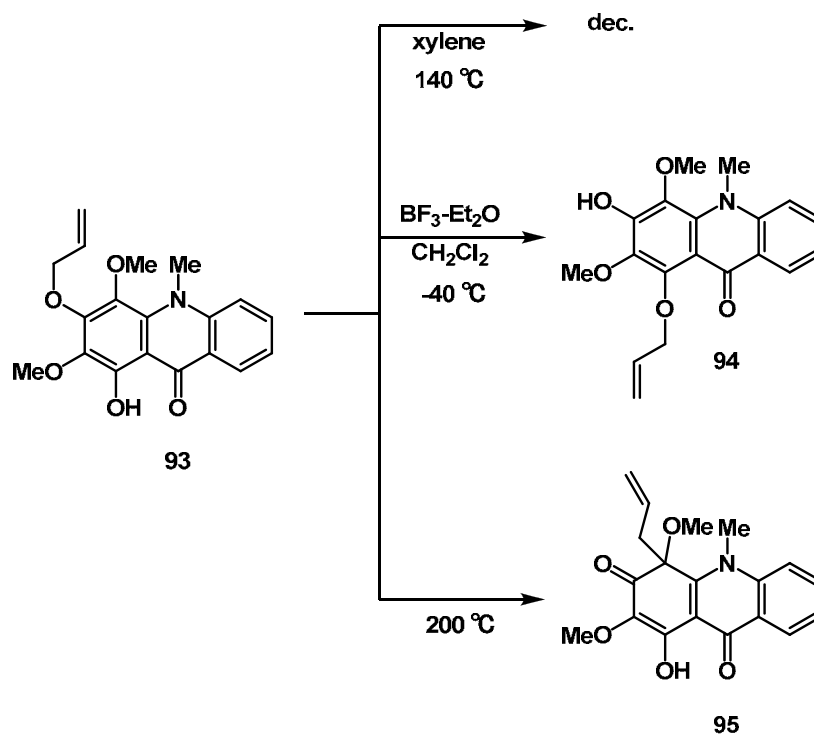
entry	conditions	result
1	xylene, 140 °C	dec.
2	xylene, K ₂ CO ₃ , 140 °C	dec.
3	pyridine, 100 °C	88
4	DMF, 120 °C	88
5	BF ₃ -Et ₂ O, 140 °C	88

そこで、3位からの Claisen 転位によるプレニル基の導入を試みることにした。実際の基質の合成にはプロパルギル基の導入やオレフィンへの還元など、Claisen 転位前駆体の合成段階で検討しなければならないことが予想されたため、アリル基を導入した化合物を用いて Claisen 転位の検討を行うことにした。化合物 **88** の Bn 基を脱保護し化合物 **92** とした後、allyl bromide を用いてアリル基を導入した化合物 **93** を合成した(Scheme 36)。



Scheme 36

この化合物 **93** に対して Claisen 転位の検討を行った (Scheme 37)。始めに、xylene 中 140 に加熱したところ、他の基質の場合と同様に分解の進行が確認された。続いて、 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ を用いた場合、1 位のフェノールにアリル基が転位した化合物 **94** が得られた。最終的に、neat、200 の条件において目的の部位にアリル基の導入された化合物 **95** を得ることができた。

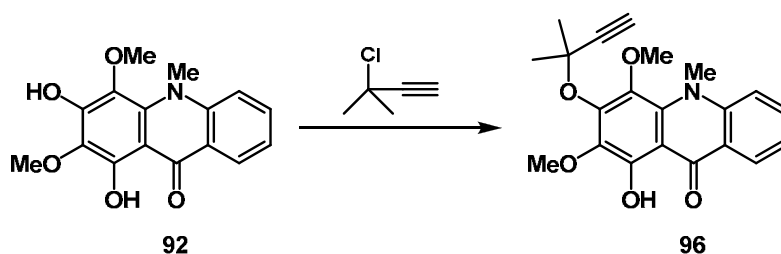


Scheme 37

Claisen 転位反応によるアリル基の 4 位への導入に成功したため、実際の基質での検討を行うこととした。

アクリドン体 **92** へのプロパルギル基の導入⁴⁹⁾を検討した (Table 10)。3-Chloro-3-methyl-1-butyne を用いて entry 1 の条件で反応を試みたところ、反応は全く進行しなかった。続いて entry 2 に示した条件で反応を行ったところ、基質の分解が進行し、目的物を得ることはできなかった。Entry 3 に示した条件において反応は速やかに進行し、目的物であるプロパルギル基体 **96** を 75% の収率で得ることに成功した。

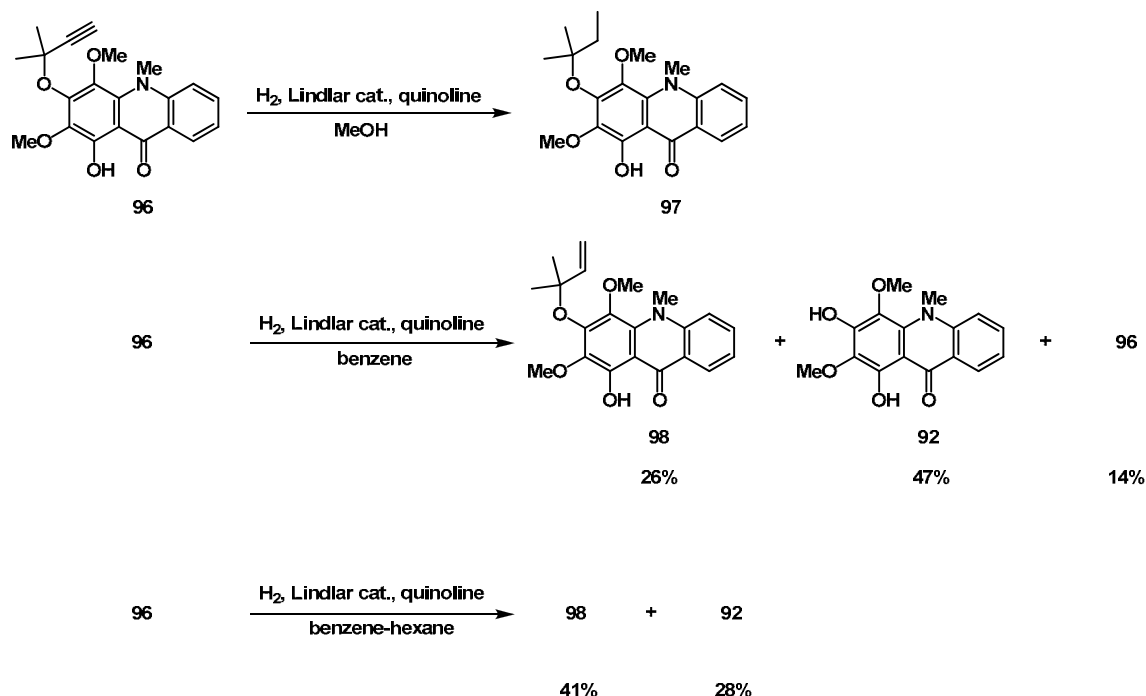
Table 10 プロパルギル基の導入の検討



entry	conditions	result (%)
1	K ₂ CO ₃ , KI/ DMF 65 °C	n.r.
2	DBU, CuCl ₂ ·2H ₂ O/ CH ₃ CN -40 →10 °C	dec.
3	K ₂ CO ₃ , KI, CuI/ acetone	75

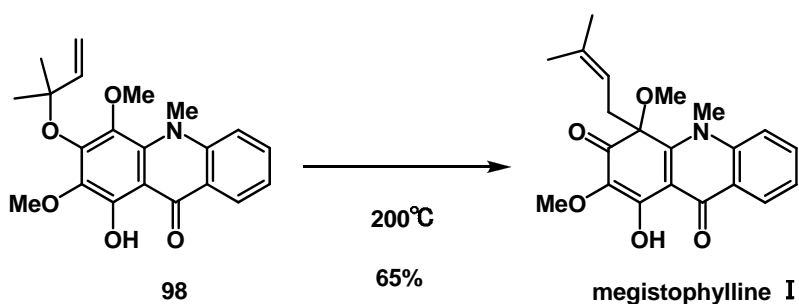
化合物 **96** に対し Pd 触媒を用いたプロパルギル基の還元反応を行った (Scheme 38)。メタノール中、化合物 **96** を Lindlar 触媒を用いた還元反応を試みたところ、過剰に反応が進行してしまい、還元体 **97** が生成するのみで目的のオレフィン体 **98** を得ることは出来なかった。続いて、ベンゼン中反応を行ったところ、目的物であるオレフィン体 **98** を得ることはできたが、26%と低収率であった。目的物以外の生成物としては化合物 **92** が 47%の収率で得られており、3 位のアルキル鎖が脱離してしまっていることが判明した。触媒を Pd/BaSO₄ へ変更し、還元反応を試みたが反応の進行が遅く、またオレフィンの生成は少量であったのに対し化合物 **92** の生成が多くみられた。反応中の TLC では生成物の減少速度が出発物質の減少速度よりも速かったため、アルキル鎖の脱離反応はオレフィンへと還元された後に起こっていることが示唆された。そのため、収率はかなり低いものの反応速度の速い Lindlar 触媒を用いて還元反応を行うこととし、さらに検討した結果、反応溶媒としてベンゼン/ヘキサン (1:5) の

系において化合物 **92** が 28%の収率で得られるが、目的物であるオレフィン体 **98** を 41%と中程度の収率で得ることが出来た。



Scheme 38

得られた Claisen 転位前駆体 **98** に対し、先の条件にて反応を行ったところ、先程と同様に一部化合物 **92** の生成を伴うものの、megistophylline の合成に成功した(Scheme 39)。



Scheme 39

合成した megistophylline の構造決定については ^1H および ^{13}C NMR スペクトルデータの一致、さらに NOE 測定によるプレニル基の導入位置の確認により行った (Figure 15)。

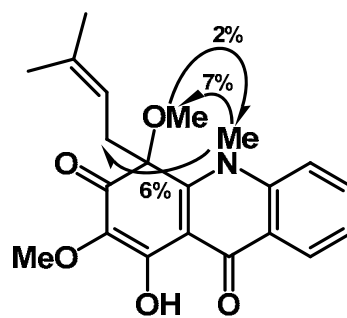


Figure 15

4 . おわりに

Methyl gallate を出発原料として、15 段階、総収率 2.3% で megistophylline の全合成を達成した。

結語

本研究では植物由来の生物活性三環性有機化合物の化学的研究を行い、以下のような知見を得た。

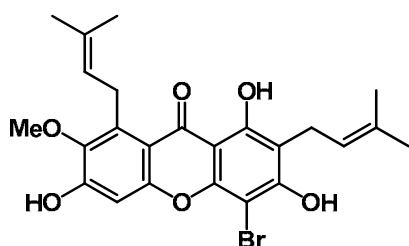
- 1) *Garcinia mangostana* Lnn. (Guttiferae)の果皮より単離したマンゴスチン類を用いて種々の誘導体合成をおこない、MRSA に対するイミペネムの抗菌活性増強作用を有する化合物 **5** を見出した。また、マンゴスチン誘導体を *m*CPBA を用いた酸化反応に付した際に得られた化合物 **8** は PDGF に誘発される HASMC の増殖抑制作用を有することを見出した。以上より天然物から誘導体を合成することにより、短段階で有用活性物質の探索が行えることが可能であることが示された。
- 2) *Sarcomelicope megistophylla* Hartley (Rutaceae)より単離されたスピロジエノン骨格を有するアクリドン型化合物である megistophylline の合成研究を行った。化合物 **5** の合成と同様に陽極酸化反応に付すことで合成できるものと考え、酸化前駆体として化合物 **17** を設定し、methyl gallate を出発物質として合成研究を行った。その結果、化合物 **17** に対する陽極酸化反応を始めとする種々の酸化反応では天然物への誘導は困難であった。続いて、Claisen 転位反応を鍵段階とした合成研究を行った結果、化合物 **98** からの Claisen 転位反応により megistophylline の全合成を 15 段階、2.3% で達成した。

Experimental section

General

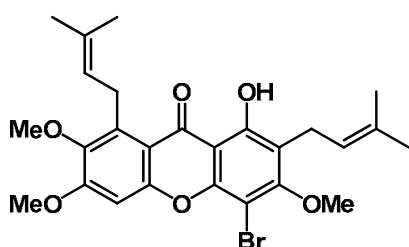
All reactions were carried out under an argon atmosphere unless otherwise noted. Melting points were measured on a Yanaco MP-S3 and uncorrected. IR spectra were recorded on JASCO A-202 Infrared Spectrophotometer. ^1H -NMR and ^{13}C NMR spectra were obtained on JEOL JNM EX-270 and JEOL JNM GX-400 spectrometers in CDCl_3 using tetramethylsilane as an internal standard, as otherwise stated. High-resolution mass spectra were obtained on JEOL JMS-700 (FAB) spectrometer and Hitachi M-80 B GC-MS (EI) spectrometer. Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical silica 60N (spherical, neutral, 63-210 μm) was used for column chromatography. Anodic oxidation was conducted using HSV-100 (Hokuto Denko) as potentiostat, a glassy carbon beaker as an anode, a platinum wire as a cathode, and a standard calomel electrode as a reference electrode.

1. Chemical modification of mangostins



4-Bromo-1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one (1):

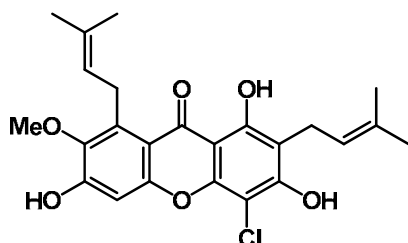
To a solution of α -mangostin (0.20 g, 0.50 mmol) in THF (3 mL) was added NBS (97 mg, 0.54 mmol) at 0 °C. After being stirred for 20 h, the mixture was poured into water and the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **1** (0.12 g, 51%) as yellow powder. IR (KBr disk), 3480, 3219, 2918, 1645, 1604 and 1575 cm^{-1} ; mp 171-172 °C; δ_{H} (ACETN), 1.69 (3H, s), 1.71 (3H, s), 1.82 (3H, s), 1.83 (3H, s), 3.45 (2H, d, $J=6.8$ Hz), 3.82 (3H, s), 4.07 (2H, d, $J=5.6$ Hz), 5.24-5.29 (2H, m), 6.36 (2H, br), 6.95 (1H, s), 13.67 (1H, s); δ_{C} (acetone- d_6), 17.9, 18.3, 22.3, 25.9, 26.6, 62.1, 86.3, 101.8, 104.2, 110.5, 111.8, 121.3, 122.8, 132.2, 133.3, 137.1, 142.9, 150.5, 154.7, 155.3, 156.6, 159.8, 181.5



4-Bromo-1-hydroxy-3,6,7-trimethoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one (2):

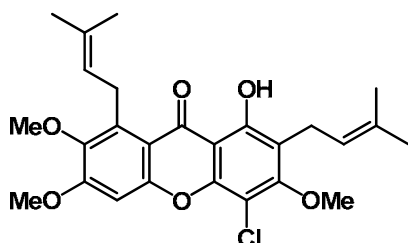
To a solution of **1** (17 mg, 0.036 mmol) in acetone (1 mL) were added K_2CO_3 (44 mg, 0.32 mmol) and MeI (10 μL , 0.16 mmol) at 0 °C. After being stirred for 16 h, the reaction was poured into water and the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/7) to give **2** (12 mg, 67%) as yellow powder. δ_{H} (CDCl_3), 1.68 (3H, s), 1.69 (3H, s), 1.81 (3H, s),

1.85 (3H, s), 3.44 (2H, d, $J=7.3$ Hz), 3.81 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 4.11 (2H, d, $J=6.8$ Hz), 5.21 (1H, t, $J=6.8$ Hz), 5.24 (1H, t, $J=7.3$ Hz), 6.89 (1H, s), 13.68 (1H, s)



4-Chloro-1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one (3):

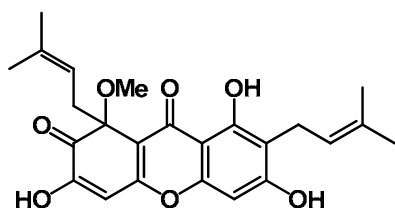
To a solution of α -mangostin (20 mg, 0.049 mmol) in benzene (2 mL) was added NCS (8.0 mg, 0.060 mmol) at room temperature. After being stirred for 23 h, the reaction was poured into water at 0 and the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **3** (10 mg, 46%) as yellow powder. IR (KBr disk), 3232, 2913, 1645, 1606 and 1456 cm^{-1} ; mp 150-151 ; δ_{H} (CDCl_3), 1.67 (3H, s), 1.69 (3H, s), 1.80 (3H, s), 1.81 (3H, s), 3.42 (2H, d, $J = 7.3$ Hz), 3.80 (3H, s), 4.06 (2H, d, $J = 5.9$ Hz), 5.22 (1H, t, $J = 5.9$ Hz), 5.25 (1H, t, $J = 7.3$ Hz), 6.34 (1H, br), 6.38 (1H, br), 6.93 (1H, s), 13.60 (1H, s); δ_{C} (CDCl_3), 17.8, 18.2, 22.0, 25.8, 26.5, 62.1, 96.4, 101.8, 104.0, 110.5, 111.9, 121.3, 122.9, 132.3, 133.3, 137.2, 143.0, 149.6, 154.9, 155.4, 155.9, 159.1, 181.7



4-Chloro-1-hydroxy-3,6,7-trimethoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one (4):

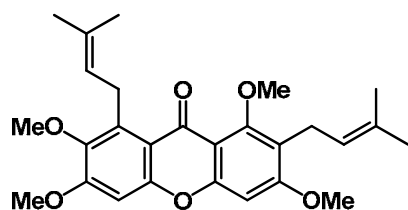
To a solution of **3** (11 mg, 0.024 mmol) in acetone (2 mL) were added K_2CO_3 (44 mg, 0.32 mmol) and MeI (10 μL , 0.16 mmol) at 0 . After being stirred for

14 h, the reaction was quenched by the addition of sat. NH_4Cl aq. and the resulting mixture was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **4** (8.7 mg, 77%) as light yellow powder. IR (KBr disk), 2913, 1598 and 1456 cm^{-1} ; mp 151-152 ; δ_{H} (CDCl_3), 1.66 (3H, s), 1.67 (3H, s), 1.79 (3H, s), 1.83 (3H, s), 3.40 (2H, d, $J=7.2\text{ Hz}$), 3.79 (3H, s), 3.92 (3H, s), 3.98 (3H, s), 4.09 (2H, d, $J=6.0\text{ Hz}$), 5.20 (2H, m), 6.87 (1H, s), 13.58 (1H, s); δ_{C} (CDCl_3), 18.0, 18.3, 22.7, 25.8, 26.0, 26.3, 56.2, 61.0, 61.4, 98.6, 103.9, 106.6, 111.6, 118.3, 122.0, 122.8, 132.0, 132.1, 137.4, 144.4, 149.8, 155.3, 158.6, 159.2, 160.3, 182.1



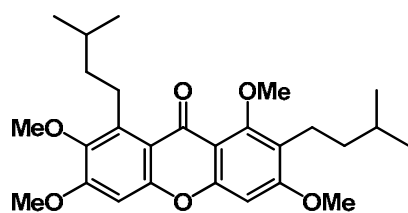
3,6,8-Trihydroxy-1-methoxy-1,7-bis(3-methylbut-2-enyl)-1H-xanthene-2,9-dione (5):

γ -mangostin (26 mg, 0.066 mmol) was electrolyzed in MeOH (6 mL) in the presence of 1M NaOH aq. (0.6 mL) and LiClO_4 (0.10 g) under CCE conditions (0.7 mA/cm^2 , 2 F/mol). After remove MeOH, added 1M HCl until pH 1. Then a mixture partitioned between CHCl_3 and H_2O . The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone/toluene, 10/1) to give **5** (14 mg, 51%) as orange powder. IR (KBr disk) 3369 , 2915 and 1644 cm^{-1} ; δ_{H} (acetone- d_6), 1.45 (3H, s), 1.55 (3H, s), 1.78 (3H, s), 1.85 (3H, s), 2.89 (1H, dd, $J=7.8, 12.7\text{ Hz}$), 3.13 (3H, s), 3.37 (1H, dd, $J=7.8, 12.7\text{ Hz}$), 3.47 (2H, d, $J=6.8\text{ Hz}$), 4.75 (1H, t, $J=7.8\text{ Hz}$), 5.28 (1H, t, $J=6.8\text{ Hz}$), 6.41 (1H, s), 6.49 (1H, s), 13.4 (1H, s); δ_{C} (acetone- d_6), 17.9, 18.0, 21.6, 25.8, 25.9, 38.5, 53.8, 83.0, 93.8, 104.6, 108.9, 110.6, 113.2, 114.3, 120.8, 136.1, 137.7, 151.8, 154.8, 159.5, 160.0, 161.3, 178.4, 199.1; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{27}\text{O}_7$ (M+H) 427.1751, found: m/z 427.1766



1,3,6,7-Tetramethoxy-2,8-bis(3-methylbut-2-enyl)-9H-xanthen-9-one (6):

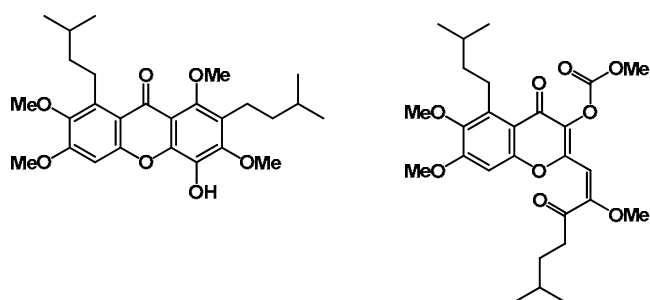
To a solution of mangostin extracts (14 g) in DMF (70 mL) were added K_2CO_3 (48 g, 0.35 mol) and MeI (30 mL, 0.48 mol) at 0 °C. After being stirred for 3 d, the reaction was poured into water and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was dissolved in DMF (50 mL) and added NaH (0.21 g, 5.3 mmol, 60% dispersion in mineral oil) and MeI (0.70 mL, 0.011 mol) at 0 °C. After being stirred for 24 h, the reaction was poured into water and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to afford a solid which was recrystallized from EtOAc-hexane to give **6** (7.0 g) as white crystals. Mp. 107-108 °C; IR (KBr disk) 2929, 1649 and 1596 cm^{-1} ; δ_H ($CDCl_3$), 1.62 (3H, s), 1.64 (3H, s), 1.77 (3H, s), 1.82 (3H, s), 3.37 (2H, d, $J=7.3$ Hz), 3.77 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.12 (2H, d, $J=6.8$ Hz), 5.16 (1H, t, $J=7.3$ Hz), 5.30 (1H, t, $J=6.8$ Hz), 6.54 (1H, s), 6.68 (1H, s); δ_C ($CDCl_3$), 17.9, 18.2, 22.4, 25.8, 25.9, 26.0, 55.8, 55.9, 60.9, 61.9, 94.2, 97.7, 110.8, 114.6, 120.4, 122.7, 123.8, 131.1, 131.3, 137.2, 143.8, 154.2, 156.9, 158.5, 162.0, 176.1; HRMS (EI) calcd for $C_{27}H_{32}O_6$ (M) 452.2199, found: m/z 452.2148



1,7-Diisopentyl-2,3,6,8-tetramethoxy-9H-xanthen-9-one (7):

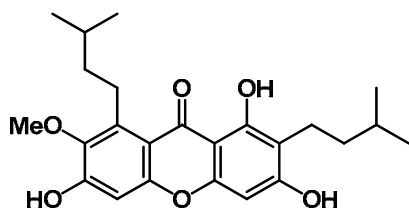
To a solution of **6** (4.7 g, 10 mmol) in MeOH (50 mL) was added 10% Pd-C, and the mixture was stirred under H_2 atmosphere at room temperature for 24 h, then the mixture was filtrated by celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **7** (4.6 g, 98%) as colorless oil. IR (film) 2954, 1650 and 1614 cm^{-1} ;

δ_{H} (CDCl₃), 0.92 (6H, d, $J=6.8$ Hz), 0.98 (6H, d, $J=6.8$ Hz), 1.35 (2H, m), 1.46 (2H, m), 1.59 (1H, m), 1.76 (1H, m), 2.62 (2H, t, $J=8.0$ Hz), 3.35 (2H, t, $J=7.8$ Hz), 3.78 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 6.49 (1H, s), 6.63 (1H, s); δ_{C} (CDCl₃), 21.1, 22.5, 22.6, 24.8, 28.4, 28.7, 39.1, 40.4, 55.7, 55.8, 61.0, 61.9, 93.9, 97.4, 110.6, 114.6, 121.7, 138.1, 143.5, 154.1, 156.1, 156.6, 158.3, 162.0, 175.9; HRMS (EI) calcd for C₂₇H₃₆O₆ (M) 456.2512, found: m/z 456.2512



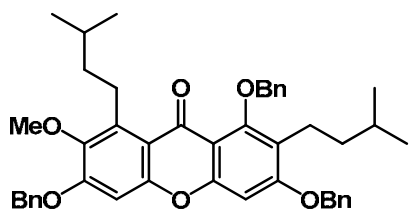
4-Hydroxy-2,8-diisopentyl-1,3,6,7-tetramethoxy-9H-xanthen-9-one (8), (E)-5-isopentyl-6,7-dimethoxy-2-(2-methoxy-6-methyl-3-oxohept-1-enyl)-4-oxo-4H-chromen-3-yl methyl carbonate (9):

To a solution of **7** (0.77 g, 1.7 mmol) in CH₂Cl₂ (2 mL) was added *m*CPBA (0.83 g, 3.4 mmol) in CH₂Cl₂ (6 mL) at 0 °C. After being stirred for 16 h, the reaction was quenched by the addition of sat. NaHCO₃ aq. at 0 °C, and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/toluene, 1/30) to give **8** (93 mg, 12%) as yellow solid and **9** (0.16 g, 19 %) as yellow oil. **8**; IR (disk): 3311, 2954, 1592, 1454 cm⁻¹; mp 156-157 °C; δ_{H} (CDCl₃), 0.94 (6H, d, $J=6.4$ Hz), 0.96 (6H, d, $J=6.4$ Hz), 1.43 (4H, m), 1.62 (2H, m), 1.75 (1H, m), 2.63 (2H, t, $J=8.0$ Hz), 3.32 (2H, t, $J=8.0$ Hz), 3.79 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 5.65 (1H, br), 6.73 (1H, s); δ_{C} (CDCl₃), 22.0, 22.5, 22.6, 25.0, 28.6, 28.8, 39.9, 40.4, 55.9, 61.1, 61.2, 62.2, 97.5, 113.3, 114.4, 125.9, 132.9, 139.4, 143.3, 143.8, 148.9, 150.6, 153.9, 157.0, 176.2; HRMS(EI) calcd for C₂₇H₃₆O₇ (M), 472.2461, found: m/z 472.2445; **9**; IR (film) 2954, 1776 and 1635 cm⁻¹; δ_{H} (CDCl₃), 0.88 (6H, d, $J=6.4$ Hz), 0.93 (6H, d, $J=6.4$ Hz), 1.37 (2H, m), 1.66 (4H, m), 2.73 (2H, t, $J=7.3$ Hz), 3.27 (2H, t, $J=7.8$ Hz), 3.77 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 3.91 (3H, s), 5.57 (1H, s), 6.47 (1H, s); δ_{C} (CDCl₃), 22.4, 22.6, 24.7, 27.6, 28.6, 32.0, 55.8, 55.9, 56.6, 61.1, 89.1, 97.5, 115.4, 132.4, 139.0, 144.6, 151.1, 152.9, 154.0, 156.9, 161.6, 171.3, 199.4



1,3,6-Trihydroxy-2,8-diisopentyl-7-methoxy-9H-xanthen-9-one (10):

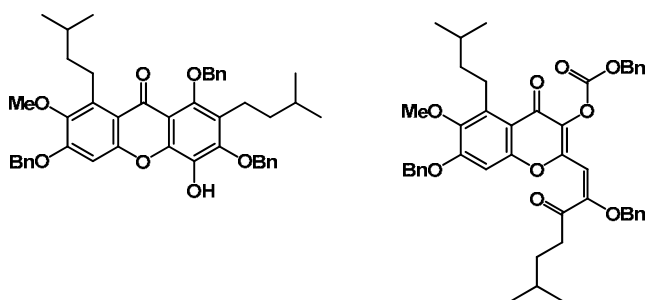
To a solution of α -mangostin (0.39 g, 0.96 mmol) in MeOH (10 mL) was added 10% Pd-C, and the mixture was stirred under H₂ atmosphere at room temperature for 6 h. Then the mixture was filtrated by celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **10** (0.40 g, 100%) as yellow oil. IR (film) 3388, 2954 and 1606 cm⁻¹; δ_{H} (actone-d₆), 0.96 (6H, d, J =6.4 Hz), 0.98 (6H, d, J =6.4 Hz), 1.44 (2H, m), 1.63 (3H, m), 1.74 (1H, m), 2.63 (2H, t, J = 8.4 Hz), 3.31 (2H, t, J =8.3 Hz), 3.82 (3H, s), 6.24 (1H, s), 6.78 (1H, s), 13.81 (1H, s); δ_{H} (actone-d₆) δ 20.2, 22.5, 22.6, 25.6, 28.3, 28.9, 38.0, 40.3, 62.3, 92.5, 101.2, 103.7, 110.8, 112.2, 139.2, 142.3, 154.2, 154.5, 155.7, 159.9, 161.0, 181.8



1,3,6-Tris(benzyloxy)-2,8-diisopentyl-7-methoxy-9H-xanthen-9-one (11):

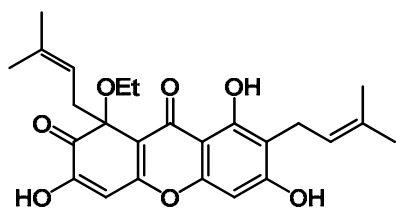
To a solution of **10** (0.40 g, 0.96 mmol) in acetone (10 mL) were added K₂CO₃ (0.79 g, 5.7 mmol) and BnBr (0.27 mL, 2.3 mmol) at 0 °C. After being stirred for 3 d, the reaction was poured into water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was dissolved in DMF (5 mL) and added NaH (76 mg, 0.19 mmol, 60% dispersion in mineral oil) and BnBr (0.15 mL, 0.12 mmol) at 0 °C. After being stirred for 14 h, the reaction was poured into water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **11** (0.31 g, 47 %) as yellow oil. IR (film) 2952, 1612 and 1594 cm⁻¹; δ_{H}

(CDCl₃), 0.85 (6H, d, *J*=6.4 Hz), 1.03 (6H, d, *J*=6.8 Hz), 1.39 (2H, m), 1.54 (3H, m), 1.83 (1H, m), 2.68 (2H, t, *J*=8.3 Hz), 3.40 (2H, t, *J*=8.3 Hz), 3.86 (3H, s), 4.98 (2H, s), 5.14 (2H, s), 5.19 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 7.33-7.67 (15H, m); δ_C (CDCl₃), 21.8, 22.6, 22.7, 25.2, 28.7, 29.1, 29.8, 38.2, 39.0, 40.3, 45.2, 61.2, 70.2, 70.5, 95.3, 98.7, 111.1, 114.9, 122.3, 126.9, 127.1, 127.2, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.0, 135.9, 136.1, 137.4, 139.4, 143.8, 153.9, 155.6, 156.1, 157.0, 160.9, 175.9



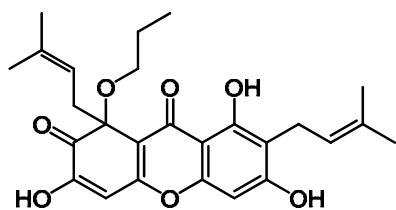
1,3,6-Tris(benzyloxy)-4-hydroxy-2,8-diisopentyl-7-methoxy-9H-xanthen-9-one (12), (E)-Benzyl 7-(benzyloxy)-2-(2-(benzyloxy)-6-methyl-3-oxohept-1-enyl)-5-isopentyl-6-methoxy-4-oxo-4H-chromen-3-yl carbonate (13):

To a solution of **11** (0.16 g, 0.23 mmol) in CH₂Cl₂ (1 mL) was added *m*CPBA (0.12 g, 0.49 mmol) in CH₂Cl₂ (3 mL) at 0 °C. After being stirred for 21 h, the reaction was quenched by the addition of sat. NaHCO₃ aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/toluene, 1/50) to give **12** (6.7 mg, 4%) as light yellow solid and **13** (15 mg, 8 %) as light yellow oil. **12**; IR (KBr disk), 3178, 2952, 2866, 1589 and 1456 cm⁻¹; mp 166-167 °C; δ_H (CDCl₃), 0.83 (6H, d, *J*=6.3 Hz), 1.02 (6H, d, *J*=6.6 Hz), 1.39 (2H, m), 1.53 (3H, m), 1.82 (1H, m), 2.60 (2H, t, *J*=7.9 Hz), 3.37 (2H, t, *J*=7.9 Hz), 3.87 (3H, s), 4.91 (2H, s), 5.14 (2H, s), 5.20 (2H, s), 5.44 (1H, br), 6.85 (1H, s), 7.44 (15H, m); **13**; δ_H (CDCl₃), 0.87 (6H, d, *J*=5.4 Hz), 0.97 (6H, d, *J*=6.4 Hz), 1.40 (2H, m), 1.58 (3H, m), 1.73 (1H, m), 2.72 (2H, t, *J*=7.3 Hz), 3.30 (2H, t, *J*=7.8 Hz), 3.82 (3H, s), 4.89 (2H, s), 5.12 (2H, s), 5.30 (2H, s), 5.64 (1H, s), 6.57 (1H, s), 7.37 (15H, m)



1-Ethoxy-3,6,8-trihydroxy-1,7-bis(3-methylbut-2-enyl)-1H-xanthene-2,9-dione (14):

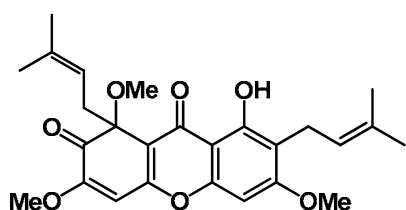
Iodobenzene (32 μ L, 0.28 mmol) was electrolyzed in $\text{CF}_3\text{CH}_2\text{OH}$ (12 mL) in the presence of LiClO_4 (0.10 g) under CCE conditions (0.3 mA/ cm^2 , 2.5 F/ mol). The reaction mixture was poured into solution of γ -mangostin (56 mg, 0.14 mmol) in EtOH (5 mL) at 0 and being stirred for 1.5 h. Then the mixture was poured into water and extracted with EtOAc three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (toluene/ acetone, 10/ 1) to give **14** (22 mg, 36%) as orange oil. IR (film), 3358, 2925, 1645, 1605 and 1457 cm^{-1} ; δ_{H} (CDCl_3), 1.11 (3H, t, $J=6.9$ Hz), 1.37 (3H, s), 1.47 (3H, s), 1.70 (3H, s), 1.77 (3H, s), 2.80 (1H, dd, $J=7.9$ Hz, 13.5 Hz), 3.04-3.10 (1H, m), 3.20-3.34 (2H, m), 3.38 (2H, d, $J=6.6$ Hz), 4.65 (1H, t, $J=7.9$ Hz), 5.21 (1H, t, $J=6.9$ Hz), 6.34 (1H, br), 6.37 (1H, s), 13.38 (1H, s); δ_{C} (CDCl_3), 15.7, 18.0, 21.6, 25.8, 25.9, 38.8, 61.9, 82.2, 90.1, 93.8, 108.7, 110.5, 113.7, 114.4, 121.0, 135.8, 137.4, 152.2, 154.7, 159.6, 159.9, 161.2, 171.5, 178.3, 199.7



3,6,8-Trihydroxy-1,7-bis(3-methylbut-2-enyl)-1-propoxy-1H-xanthene-2,9-dione (15)

Iodobenzene (32 mL, 0.28 mmol) was electrolyzed in $\text{CF}_3\text{CH}_2\text{OH}$ (12 mL) in the presence of LiClO_4 (0.10 g) under CCE conditions (0.3 mA/ cm^2 , 2.5 F/ mol). Reaction mixture was poured into solution of γ -mangostin (47 mg, 0.12 mmol) in *n*PrOH (5 mL) at 0 and being stirred for 16 h. Then the reaction mixture was poured into water and extracted with EtOAc three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone

/toluene, 1/10) to give **15** (22 mg, 41%) as orange oil. IR (film), 3349, 2927, 1645, 1604 and 1458 cm^{-1} ; δ_{H} (CDCl_3), 0.34 (3H, t, $J=7.3$ Hz), 1.45 (3H, s), 1.54 (3H, s), 1.58 (2H, m), 1.77 (3H, s), 1.85 (3H, s), 2.88 (1H, dd, $J=7.3$ Hz, 12.7 Hz), 2.96 (1H, m), 3.22 (1H, m), 3.44 (1H, dd, $J=7.3$ Hz, 12.7 Hz), 3.46 (2H, d, $J=6.3$ Hz), 4.71 (1H, t, $J=7.3$ Hz), 5.28 (1H, t, $J=6.3$ Hz), 6.42 (1H, s), 6.47 (1H, s), 6.50 (1H, br), 6.88 (1H, br), 13.45 (1H, s); δ_{C} (CDCl_3), 10.5, 18.0, 21.6, 23.2, 25.8, 25.9, 38.6, 68.2, 82.0, 93.8, 104.7, 108.8, 110.5, 114.0, 114.4, 120.9, 135.9, 137.5, 151.7, 154.8, 159.6, 159.6, 161.2, 178.4, 199.5



8-Hydroxy-1,3,6-trimethoxy-1,7-bis(3-methylbut-2-enyl)-1H-xanthene-2,9-dione (16):

To a solution of **5** (53 mg, 0.12 mmol) in DMF (2 mL) were added K_2CO_3 (0.12 g, 0.84 mmol) and MeI (26 μL , 0.40 mmol) at 0 . After being stirred for 20h, the reaction mixture was quenched by the addition of water and the resulting mixture was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **16** (37 mg, 66%) as yellow oil. IR (film), 2926, 1698, 1649, 1593 and 1447 cm^{-1} ; δ_{H} (CDCl_3), 1.43 (3H, s), 1.52 (3H, s), 1.66 (3H, s), 1.77 (3H, s), 2.84 (1H, dd, $J=8.6$, 13.2 Hz), 3.10 (3H, s), 3.25 (1H, dd, $J=7.3$, 13.2 Hz), 3.34 (2H, d, $J=6.8$ Hz), 3.85 (3H, s), 3.89 (3H, s), 4.77 (1H, t, $J=8.0$ Hz), 5.20 (1H, t, $J=6.8$ Hz), 6.17 (1H, s), 6.37 (1H, s), 13.05 (1H, s)

In vitro Assay for Potential of Imipenem Activity Against Methicillin-Resistant *Staphylococcus Aureus*:

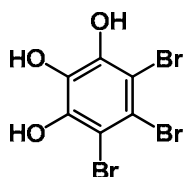
MRSA (2.0×10^7 CFU) was spread on the HMA medium in a plastic plate (10 \times 14 cm, Eikiken Kizai Co) containing Mueller–Hinton broth and 1.5% agar plate with or without imipenem at 10 $\mu\text{g}/\text{mL}$ (HMA+IMP plate or HMA plate, respectively), which concentration has no effect on MRSA growth. Paper disks (Advantec) containing a sample (10 μg) were placed on the HMA+IMP and HMA plate, and incubated at 37 $^\circ\text{C}$ for 20 h. Anti-MRSA activity was expressed as

diameter [mm] of the inhibitory zone on the plates. If the sample potentiates the imipenem activity, larger inhibitory zone is observed on the HMA+IMP plate than on the HMA plate.

In vitro Assay for inhibitory activity on PDGF-induced HASMC proliferation:

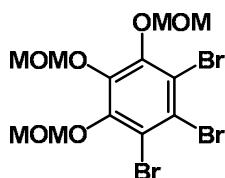
Cell proliferation was determined by [³H]-thymidine incorporation. HASMC were incubated for 20 hours with or without PDGF-BB (20 ng/mL) and indicated concentrations of mangostins and its derivatives and then pulse-labeled with 1 μCi/mL of [³H]-thymidine for 4 hours. Cells were harvested using a Universal Harvester (Perkin Elmer), and then transferred to a GF/C filter (Perkin Elmer). The filter was dried and counted in scintillation fluid using a Microplate Scintillation and Luminescence Counter-Topcount NXT (Perkin Elmer).

2. Synthetic studies of megistophylline



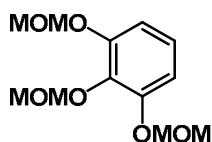
4,5,6-Tribromobenzene-1,2,3-triol:

To a solution of pyrogallol (2.3 g, 18 mmol) in AcOH (9 mL) and CHCl₃ (9 mL) was added Br₂ (2.8 mL, 54 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was poured into water and appeared precipitate was filtrate and precipitate was washed with CHCl₃ to give 4,5,6-tribromobenzene-1,2,3-triol (0.34 g, 64%) as colorless solid. δ_{H} (acetone-d₆), 8.50 (3H, br)



1,2,3-Tribromo-4,5,6-tris(methoxymethoxy)benzene (21):

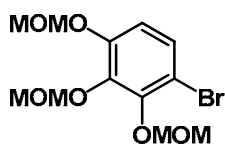
To a solution of 4,5,6-tribromobenzene-1,2,3-triol (0.33 g, 0.91 mmol) in acetone (5 mL) were added MOMCl (0.23 mL, 3.0 mmol) and K₂CO₃ (0.88 g, 6.3 mmol) at 0 °C. After being stirred for 2 h, the reaction was poured into water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **21** (0.44 g, 99%) as colorless oil. IR (film), 3458, 3336, 2940, 2835, 1615 and 1575 cm⁻¹; δ_{H} (CDCl₃), 3.55 (3H, s), 3.63 (6H, s), 5.11 (2H, s), 5.17 (4H, s); δ_{C} (CDCl₃), 58.0, 58.5, 99.3, 99.6, 117.4, 123.3, 143.3, 148.8



1,2,3-Tris(methoxymethoxy)benzene (23):

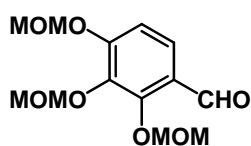
To a solution of pyrogallol (0.90 g, 7.1 mmol) in CH₂Cl₂ (40 mL) were added MOMCl (1.9 mL, 0.025 mol) and *i*Pr₂NEt (8.5 mL, 0.050 mol) at 0 °C. After being stirred for 6 h, the reaction was quenched by the addition of sat. NH₄Cl aq.

at 0 °C and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/8) to give **23** (1.3 g, 68%) as colorless oil. IR (film), 2956, 2901, 2826, 1597 and 1475 cm⁻¹; δ_{H} (CDCl₃), 3.48 (6H, s), 3.60 (3H, s), 5.13 (2H, s), 5.18 (4H, s), 6.82 (2H, d, *J*=8.4 Hz), 6.94 (1H, t, *J*=8.4 Hz); δ_{C} (CDCl₃), 56.2, 57.1, 95.2, 98.5, 110.3, 124.1, 136.4, 151.1



1-Bromo-2,3,4-tris(methoxymethoxy)benzene (**22**):

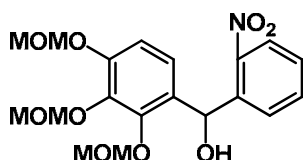
To a solution of **23** (0.50 g, 2.0 mmol) in THF (10 mL) was added NBS (0.35 mg, 2.0 mmol) at 0 °C. After being stirred for 16 h, the reaction was poured into water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/6) to give **22** (0.53 g, 80%) as colorless oil. IR (film), 2902 and 2828, 1576 and 1472 cm⁻¹; δ_{H} (CDCl₃), 3.47 (3H, s), 3.58 (3H, s), 3.64 (3H, s), 5.12 (2H, s), 5.15 (2H, s), 5.18 (2H, s), 6.84 (1H, d, *J*=9.0 Hz), 7.20 (1H, d, *J*=9.0 Hz); δ_{C} (CDCl₃), 56.3, 57.5, 58.2, 95.2, 98.8, 99.3, 110.0, 112.9, 127.5, 150.8,



2,3,4-Tris(methoxymethoxy)benzaldehyde (**24**):

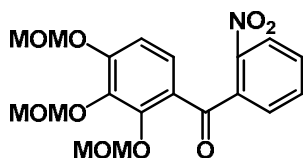
To a solution of **23** (0.12 g, 0.46 mmol) in THF (5 mL) was added a solution of *n*BuLi (0.35 mL, 0.56 mmol, 1.6 M in hexane) at 0 °C. After being stirred for 30 min at room temperature, added excess amount of DMF at 0 °C to reaction mixture. After being stirred for 1 h, the reaction was quenched by the addition of sat. NH₄Cl aq., then the resulting slurry was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **24** (0.10 g, 76%) as light yellow solid. IR (KBr disk), 3134, 1645, 1616 and 1502 cm⁻¹; δ_{H} (CDCl₃), 3.48

(3H, s), 3.55 (3H, s), 3.59 (3H, s), 5.12 (2H, s), 5.24 (2H, s), 5.25 (2H, s), 7.01 (1H, d, $J=8.9$ Hz), 7.58 (1H, d, $J=8.9$ Hz), 10.26 (1H, s); δ_C (CDCl₃), 56.6, 57.5, 58.1, 94.7, 98.7, 100.2, 111.3, 124.5, 124.8, 138.7, 154.1, 156.5, 188.8



(2-Nitrophenyl)(2,3,4-tris(methoxymethoxy)phenyl)methanol (pre-25):

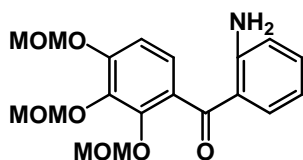
To a solution of **24** (56 mg, 0.20 mmol) in THF (1 mL) was added PhLi in cyclohexane-diethyl ether (1.05 M, 0.38 mL) at -78 °C. After being stirred for 5 min, 2-bromoanisole (80 mg, 0.39 mmol) in THF (1 mL) was added at -78 °C. After being stirred for 30 min, the reaction was quenched by the addition of sat. NH₄Cl aq. and resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **pre-25** (86 mg) as colorless oil. δ_H (CDCl₃), 3.45 (3H, s), 3.54 (3H, s), 3.57 (3H, s), 3.95 (1H, d, $J=3.6$ Hz), 5.11 (2H, s), 5.14 (2H, s), 5.17 (2H, s), 6.50 (1H, d, $J=8.8$ Hz), 6.71 (1H, d, $J=3.6$ Hz), 6.79 (1H, d, $J=8.8$ Hz), 7.45 (1H, t, $J=7.6$ Hz), 7.67 (1H, t, $J=8.0$ Hz), 7.97 (2H, m)



(2-Nitrophenyl)(2,3,4-tris(methoxymethoxy)phenyl)methanone (25):

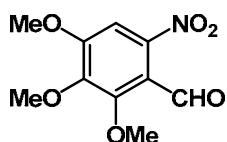
To a solution of **pre-25** (86 mg) in toluene (1 mL) and DMSO (1 mL) was added IBX (0.14 g, 0.34 mmol) at room temperature. After being stirred for 13 h, the reaction was quenched by the addition of sat. NaHCO₃ aq. at 0 °C and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/2) to give **25** (76 mg, 95% in 2 steps) as yellow oil. IR (film), 2908, 2829, 1669 and 1589 cm⁻¹; δ_H (CDCl₃), 3.30 (3H, s), 3.46 (3H, s), 3.55 (3H, s), 4.96 (2H, s), 5.10 (2H, s), 5.22 (2H, s), 6.92 (1H, d, $J=8.8$ Hz), 7.35 (1H, d, J

=8.8 Hz), 7.42 (1H, dd, $J=7.4, 1.2$ Hz), 7.57 (1H, td, $J=7.4, 1.2$ Hz), 7.68 (1H, t, $J=7.6$ Hz), 8.09 (1H, d, $J=7.6$ Hz); δ_C (CDCl₃), 56.5, 57.4, 57.6, 94.6, 98.8, 99.9, 110.4, 124.0, 124.4, 127.9, 128.7, 129.9, 133.5, 137.9, 139.5, 146.6, 151.4, 155.7, 190.7



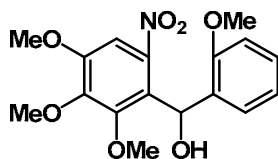
(2-Aminophenyl)(2,3,4-tris(methoxymethoxy)phenyl)methanone (26):

To a solution of **25** (9.6 mg, 0.023 mmol) in EtOH (1 mL) and water (1 mL) were added NH₄Cl (25 mg, 0.46 mmol) and Fe powder (13 mg, 0.23 mmol) at room temperature, and the mixture was heated under reflux for 2 h. The resulting slurry was filtered through a celite pad. The filtrate was extracted with EtOAc three times. The residue was purified by silica gel column chromatography (EtOAc/toluene, 1/3) to give **26** (6.7 mg, 76%) as yellow oil. IR (film), 3459, 3343, 2927, 1616 and 1587 cm⁻¹; δ_H (CDCl₃), 3.21 (3H, s), 3.51 (3H, s), 3.61 (3H, s), 5.01 (2H, s), 5.17 (2H, s), 5.24 (2H, s), 6.31 (2H, br), 6.54 (1H, t, $J=8.1$ Hz), 6.65 (1H, d, $J=8.1$ Hz), 6.99 (1H, s), 7.24 (2H, m), 7.36 (1H, dd, $J=8.1, 1.4$ Hz)



2,3,4-Trimethoxy-6-nitrobenzaldehyde (28):

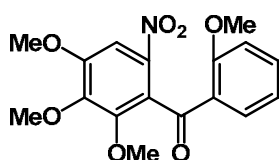
To a solution of 2,3,4-trimethoxybenzaldehyde (5.2 g, 0.027 mol) in AcOH (50 mL) was added HNO₃ (5.5 mL) dropwise at room temperature. After being stirred for 2 h at 65 °C, the reaction was poured into ice water and filtrate precipitate **28** (2.4 g, 38%) as yellow crystals. δ_H (CDCl₃), 3.95 (6H, s), 3.96 (3H, s), 7.28 (1H, s), 10.22 (1H, s)



(2-Methoxyphenyl)(2,3,4-trimethoxy-6-nitrophenyl)methanol (pre-29):

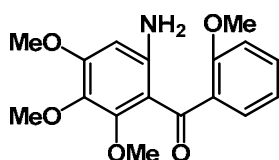
To a solution of 2-bromoanisole (1.5 g, 1.9 mmol) in THF (10 mL) was added

*n*BuLi in hexane (1.6 M, 0.71 mL, 1.1 mmol) at -78 °C. After being stirred for 20 min at room temperature, **28** (0.23 g, 0.94 mmol) in THF (5 mL) was added at -78 °C. After being stirred for 18 h, the reaction was quenched by the addition of sat. NH₄Cl aq. at 0 °C and resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **pre-29**. δ_{H} (CDCl₃), 3.53 (3H, s), 3.62 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.46 (1H, d, *J* = 10.2 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 7.01 (1H, t, *J* = 7.6 Hz), 7.08 (1H, s), 7.22 (1H, t, *J* = 7.6 Hz), 7.55 (1H, d, *J* = 7.6 Hz)



(2-Methoxyphenyl)(2,3,4-trimethoxy-6-nitrophenyl)methanone (29):

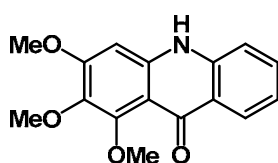
To a solution of **pre-29** in toluene (3 mL) and DMSO (3 mL) was added IBX (0.53 g, 1.9 mmol) at room temperature. After being stirred for 4.5 h, the reaction was quenched by the addition of sat. NaHCO₃ aq. and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **29** (0.13 g, 40% in 2 steps) as yellow needles. IR (KBr disk), 3298, 3118, 2944, 2846, 2617, 1658 and 1598 cm⁻¹; mp 119-120 °C; δ_{H} (CDCl₃), 3.56 (3H, s), 3.69 (3H, s), 3.95 (3H, s), 6.87 (1H, d, *J* = 8.8 Hz), 7.03 (1H, t, *J* = 8.8 Hz), 7.48 (1H, td, *J* = 8.8, 1.6 Hz), 7.54 (1H, s), 7.98 (1H, dd, *J* = 8.8, 1.6 Hz); δ_{C} (CDCl₃), 55.8, 56.5, 61.1, 61.8, 103.2, 112.0, 120.7, 125.7, 129.1, 131.2, 134.8, 139.9, 147.7, 149.8, 152.5, 159.3, 189.1



(6-Amino-2,3,4-trimethoxyphenyl)(2-methoxyphenyl)methanone (30):

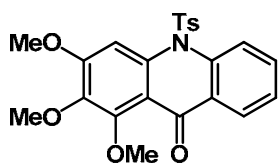
To a solution of **29** (0.31 g, 0.89 mmol) in EtOH (2.5 mL) and H₂O (0.5 mL) were added Fe powder (0.15 g, 2.7 mmol) and NH₄Cl (0.29 g, 5.4 mmol) at room

temperature. After being stirred for 1 d at 65 °C, the reaction was cooled to room temperature and filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/CHCl₃, 1/40) to give **30** (0.19 g, 67%) as yellow oil. IR (film), 3567, 3076, 2947 and 1520 cm⁻¹; δ_H (CDCl₃), 3.27 (3H, s), 3.65 (3H, s), 3.74 (3H, s), 3.84 (3H, s), 5.91 (2H, br), 6.89 (1H, d, *J* = 8.0 Hz), 6.94 (1H, t, *J* = 8.0 Hz), 7.22-7.34 (3H, m); δ_C (CDCl₃), 55.5, 55.6, 60.6, 60.8, 94.0, 109.3, 110.8, 120.0, 127.5, 130.1, 132.6, 134.2, 148.2, 155.4, 156.3, 158.5, 195.7



1,2,3-Trimethoxyacridin-9(10H)-one (**31**):

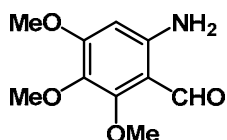
To a solution of **30** (0.13 g, 0.42 mmol) in DMSO (2 mL) was added NaH (20 mg, 0.50 mmol, 60% dispersion in mineral oil) at 0 °C. After being stirred for 1 d at 90 °C, the reaction mixture was quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH /CHCl₃, 1/50) to give **31** (82 mg, 69%) as light yellow solid. IR (KBr disk), 3420, 3133, 2989, 1635 and 1601 cm⁻¹; δ_H (CDCl₃), 3.72 (3H, s), 3.80 (3H, s), 3.97 (3H, s), 6.78 (1H, s), 7.13 (1H, t, *J* = 8.1 Hz), 7.50-7.52 (2H, m), 8.39 (1H, d, *J* = 8.1 Hz), 11.05 (1H, br)



1,2,3-Trimethoxy-10-tosylacridin-9(10H)-one (**32**):

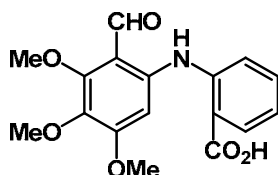
To a solution of **31** (15 mg, 0.051 mmol) in DMF (2 mL) were added TsCl (29 mg, 0.15 mmol) and NaH (20 mg, 0.05 mmol, 60% dispersion in mineral oil) at 0 °C. After being stirred for 1 h at room temperature, the reaction was cooled to 0 °C and the reaction was quenched by sat. NH₄Cl aq. Then the resulting slurry was extracted with Et₂O three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The

residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **32** (18 mg, 80%) as yellow oil. IR (film), 2925, 1653 and 1496 cm^{-1} ; δ_{H} (CDCl_3), 2.43 (3H, s), 3.81 (3H, s), 3.98 (3H, s), 4.02 (3H, s), 7.18-7.28 (3H, m), 7.60-7.70 (4H, m), 8.02 (1H, d, $J=8.8\text{Hz}$); δ_{C} (CDCl_3), 21.8, 61.4, 61.6, 102.9, 113.1, 119.9, 122.6, 124.9, 128.0, 128.7, 129.6, 130.1, 133.3, 142.7, 145.3, 145.9, 148.1, 149.0, 149.2, 157.0



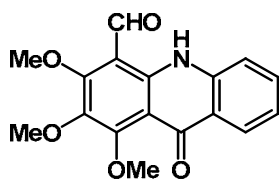
6-Amino-2,3,4-trimethoxybenzaldehyde (**35**):

To a solution of **28** (0.16 g, 0.65 mmol) in MeOH (3 mL) were added 10% Pd-C and HCOONH_4 at room temperature. After being stirred for 3.5 h, the resulting slurry was filtered through a celite pad. The filtrate was extracted with EtOAc three times. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **35** (68 mg, 50%) as colorless solid. IR (KBr disk), 3455, 3364, 2937, 2837, 1602 and 1487 cm^{-1} ; δ_{H} (CDCl_3), 3.70 (3H, s), 3.73 (3H, s), 3.87 (3H, s), 5.72 (1H, s), 6.29 (2H, br), 10.00 (1H, s)



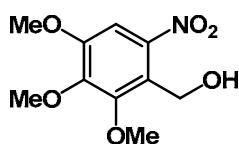
2-(2-Formyl-3,4,5-trimethoxyphenylamino)benzoic acid (**34**):

To a solution of **35** (5.6 mg, 0.027 mmol) in 2-propanol were added 2-iodobenzoic acid (26 mg, 0.11 mmol), K_2CO_3 (22 mg, 0.16 mmol) and CuCl (7.9 mg, 0.080 mmol) at room temperature. After being stirred for 1.5 d at 80 $^\circ\text{C}$, the reaction mixture was quenched by the addition of sat. NH_4Cl aq. and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH / CHCl_3 , 1/20) to give **34** (2.8 mg, 32%) as yellow oil. IR (film), 2938, 1646, 1608 and 1580 cm^{-1} ; δ_{H} (CDCl_3), 3.78 (3H, s), 3.79 (3H, s), 3.98 (3H, s), 6.68 (1H, s), 7.02 (1H, t, $J=7.2\text{ Hz}$), 7.43 (1H, t, $J=8.4\text{ Hz}$), 7.60 (1H, d, $J=8.4\text{ Hz}$), 8.11 (1H, d, $J=7.2\text{ Hz}$), 10.21 (1H, s), 11.59 (1H, br)



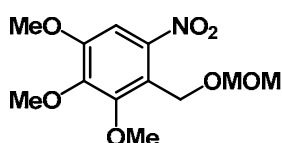
1,2,3-Trimethoxy-9-oxo-9,10-dihydroacridine-4-carbaldehyde (33), (36):

To a solution of **34** (6.5 mg, 0.020 mmol) in CH₂Cl₂ (0.1 mL) was added TFAA (27 μL, 0.20 mmol) at room temperature. After being stirred for 3 d, the reaction solvent and reagent were concentrated by *vacuo*. The residue was purified by PTLC (EtOAc/hexane, 1/2) to give **33** (1.1 mg, 18%) as yellow oil and **36** (2.2 mg) as yellow oil. **33**; IR (film); 3001, 2948, 2854, 1633, 1602, 1490 and 1462 cm⁻¹; δ_H (CDCl₃), 3.89 (3H, s), 4.15 (3H, s), 4.21 (3H, s), 7.27 (1H, t, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 8.8 Hz), 7.62 (1H, t, *J* = 8.8 Hz), 8.37 (1H, d, *J* = 8.8 Hz), 10.40 (1H, s), 12.6 (1H, br); **36**; IR (film); 3419, 2937, 1627, 1600, 1489 and 1461 cm⁻¹; δ_H (CDCl₃), 3.31 (3H, s), 3.81 (3H, s), 4.01 (3H, s), 7.32 (1H, t, *J* = 8.4 Hz), 7.36 (1H, s), 7.50 (1H, s), 7.79 (1H, t, *J* = 8.4 Hz), 7.88 (1H, d, *J* = 8.4 Hz), 8.49 (1H, d, *J* = 8.4 Hz)



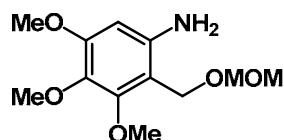
(2,3,4-Trimethoxy-6-nitrophenyl)methanol (37):

To a solution of **28** (0.45 g, 1.9 mmol) in MeOH (10 mL) was added excess amounts of NaBH₄ at 0 °C. After being stirred for 1 h, the reaction was quenched by the addition of water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was recrystallized from EtOAc-hexane to give **37** (0.43 g, 95%) as light yellow needles. IR (KBr disk), 3567, 3076, 2947 and 1520 cm⁻¹; mp 70-71 °C; δ_H (CDCl₃), 2.89 (1H, t, *J* = 7.6 Hz), 3.94 (3H, s), 3.96 (3H, s), 3.97 (3H, s), 4.78 (2H, d, *J* = 7.6 Hz), 7.38 (1H, s); δ_C (CDCl₃), 55.6, 56.4, 61.2, 62.4, 90.1, 104.4, 123.9, 144.5, 147.3, 152.6



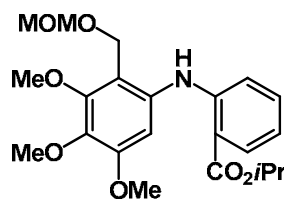
1,2,3-Trimethoxy-4-((methoxymethoxy)methyl)-5-nitrobenzene (38):

To a solution of **37** (0.20 g, 0.83 mmol) in THF (4 mL) were added MOMCl (69 μ L, 0.91 mmol) and NaH (73 mg, 1.8 mmol, 60% dispersion in mineral oil) at 0 $^{\circ}$ C. After being stirred for 3 h at 50 $^{\circ}$ C, the reaction was cooled to 0 $^{\circ}$ C and the reaction was quenched by the addition of water. Then the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/6) to give **38** (0.20 g, 84%) as yellow oil. δ_{H} (CDCl₃), 3.37 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 4.67 (2H, s), 4.79 (2H, s), 7.26 (1H, s); δ_{C} (CDCl₃), 55.5, 56.3, 59.8, 61.0, 62.0, 96.7, 104.4, 119.9, 145.1, 146.2, 152.7, 152.8



3,4,5-Trimethoxy-2-((methoxymethoxy)methyl)aniline (**38**):

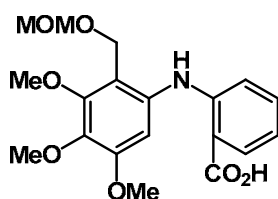
To a solution of **38** (0.18 g, 0.61 mmol) in MeOH (3 mL) were added 10% Pd-C and HCOONH₄ (0.19 g, 3.1 mmol) at room temperature. After being stirred for 2.5 h, the resulting slurry was filtered through a celite pad. The filtrate was extracted with EtOAc three times. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **39** (0.16 g, quant.) as colorless oil. IR (film), 2945, 1685, 1594 and 1542 cm^{-1} ; δ_{H} (CDCl₃), 3.39 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 3.96 (3H, s), 4.60 (2H, s), 4.63 (2H, s), 6.02 (1H, s); δ_{C} (CDCl₃), 55.5, 55.7, 60.2, 61.0, 61.6, 95.1, 95.6, 107.7, 134.2, 143.1, 152.9, 153.9



Isopropyl 2-(3,4,5-trimethoxy-2-((methoxymethoxy)methyl)phenylamino)benzoate (**40**):

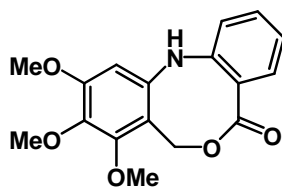
To a solution of **39** (34 mg, 0.13 mmol) in 2-propanol (2 mL) were added 2-iodobenzoic acid (98 mg, 0.40 mmol), K₂CO₃ (73 mg, 0.53 mmol) and CuCl (26 mg, 0.26 mmol) at room temperature. After being stirred for 19 h at 80 $^{\circ}$ C, the reaction mixture was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine,

dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **40** (16 mg, 29%) as orange solid. δ_{H} (CDCl_3), 1.50 (6H, d, $J=6.3$ Hz), 3.38 (3H, s), 3.93 (3H, s), 3.97 (3H, s), 4.02 (3H, s), 4.72 (2H, s), 4.88 (1H, m), 5.17 (2H, s), 7.05 (1H, d, $J=7.9$ Hz), 7.12 (1H, t, $J=7.9$ Hz), 7.29 (1H, s), 7.55 (1H, td, $J=7.9$, 1.6 Hz), 8.20 (1H, dd, $J=7.9$, 1.6 Hz), 11.22 (1H, br)



2-(3,4,5-Trimethoxy-2-((methoxymethoxy)methyl)phenylamino)benzoic acid (41):

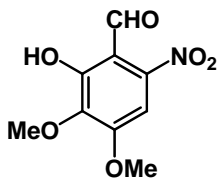
To a solution of **39** (27 mg, 0.11 mmol) in 2-propanol (2 mL) were added 2-iodobenzoic acid (52 mg, 0.21 mmol), KOAc (22 mg, 0.42 mmol), Et_3N (29 μL , 0.21 mmol) and catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ at room temperature. After being stirred for 2 d at 80 $^\circ\text{C}$, the reaction mixture was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH / CHCl_3 , 1/30) to give **41** (19 mg, 47%) as orange oil. IR (film), 3324, 2955, 1671 and 1571 cm^{-1} ; δ_{H} (CDCl_3), 3.39 (3H, s), 3.78 (3H, s), 3.86 (3H, s), 3.93 (3H, s), 4.58 (2H, s), 4.75 (2H, s), 6.73 (1H, t, $J=7.8$ Hz), 6.78 (1H, s), 7.11 (1H, d, $J=8.3$ Hz), 7.31 (1H, t, $J=8.3$ Hz), 8.01 (1H, d, $J=7.8$ Hz), 9.47 (1H, br)



8,9,10-trimethoxy-7,12-dihydro-5H-dibenzo[c,f][1,5]oxazocin-5-one (43):

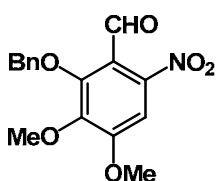
To a solution of **41** (6.6 mg, 0.018 mmol) in CH_2Cl_2 (0.1 mL) was added TFAA (24 μL , 0.18 mmol) at 0 $^\circ\text{C}$. After being stirred for 2.5 h, the reaction solvent and reagent were concentrated by *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/4) to give **43** (5.6 mg, 98%) as yellow oil. δ_{H} (CDCl_3), 3.88 (3H, s), 3.89 (3H, s), 3.96 (3H, s), 4.79 (1H, d, J

=12.7 Hz), 5.06 (1H, d, J =12.7 Hz), 6.84 (1H, s), 7.14 (1H, t, J =7.6 Hz), 7.49 (1H, d, J =7.6 Hz), 7.56 (1H, t, J =7.6 Hz), 8.09 (1H, d, J =7.6 Hz)



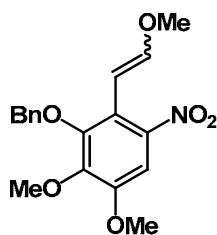
2-Hydroxy-3,4-dimethoxy-6-nitrobenzaldehyde (**44**):

To a solution of **28** (0.65 g, 2.7 mmol) in CH_2Cl_2 (15 mL) was added BBr_3 (3.0 mL, 3.0 mmol, 1.0 M in CH_2Cl_2) at -78°C . After being stirred for 15 h, the reaction was poured into ice water and the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **44** (0.55 g, 91%) as yellow oil. δ_{H} (CDCl_3), 3.99 (3H, s), 4.03 (3H, s), 7.28 (1H, s), 10.29 (1H, s), 12.44 (1H, s)



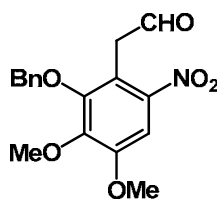
2-(Benzyloxy)-3,4-dimethoxy-6-nitrobenzaldehyde (**45**):

To a solution of **44** (0.55 g, 2.4 mmol) in DMF (10 mL) were added BnBr (0.31 mL,) and K_2CO_3 (1.0 g, 7.2 mmol) at 0°C . After being stirred for 1 d at room temperature., the reaction was cooled to 0°C and the reaction was quenched by sat. NH_4Cl aq. and the resulting slurry was extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **45** (0.75 g, 97%) as light brown prism. IR (KBr disk), 3100, 2983, 2945, 2887, 1685 and 1594 cm^{-1} ; mp $144\text{--}145^\circ\text{C}$; δ_{H} (CDCl_3), 3.89 (3H, s), 8.90 (3, s), 5.07 (2H, s), 7.22-7.31 (6H, m), 9.97 (1H, s); δ_{C} (CDCl_3), 56.7, 61.3, 103.8, 121.3, 128.5, 128.6, 128.7, 135.6, 143.2, 146.8, 151.6, 155.6, 186.7



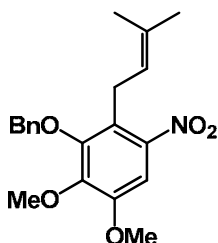
3-(Benzyloxy)-1,2-dimethoxy-4-(2-methoxyvinyl)-5-nitrobenzene (pre-46):

To a suspension of $\text{Ph}_3\text{P}^+\text{CH}_3\text{OCH}_2\text{Cl}^-$ (5.3 g, 15 mmol) in THF (15 mL) was added *t*BuOK (1.4 g, 12 mmol) in THF (12 mL) at 0 °C. After being stirred for 10 min at 0 °C, **45** (0.49 g, 1.5 mmol) in THF (8 mL) was added at 0 °C. After being stirred for 3.5 h, the reaction was quenched by the addition of sat. NH_4Cl aq. at 0 °C and resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **pre-46** (0.32 g, 61%) as *E-Z* mixture.



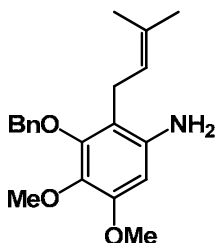
2-(2-(Benzyloxy)-3,4-dimethoxy-6-nitrophenyl)acetaldehyde (**46**):

To a solution of **pre-46** (0.32g, 0.94 mmol) in THF (3 mL) was added conc. HCl at 0 °C. After being stirred for 30 min, the reaction mixture was poured into water room temperature the resulting mixture was extracted with CHCl_3 three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **46** (0.26 g, 84%) as light yellow needles. IR (KBr disk), 2944, 2839, 1718 and 1521 cm^{-1} ; mp 87-88 °C; δ_{H} (CDCl_3), 3.97 (3H, s), 3.98 (3H, s), 4.00 (2H, s), 5.02 (2H, s), 7.35-7.36 (5H, m), 7.52 (1H, s), 9.62 (1H, s)



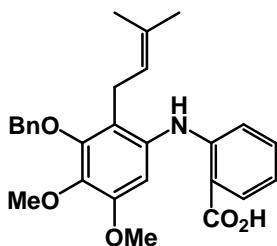
3-(Benzyloxy)-1,2-dimethoxy-4-(3-methylbut-2-enyl)-5-nitrobenzene (**47**):

To a suspension of $i\text{-PrPh}_3\text{P}^+\text{I}^-$ (0.83 g) in THF (3 mL) was added $n\text{BuLi}$ in hexane (1.6 M, 0.98 mL) at 0 °C. After being stirred for 1.5 h, **46** (64 mg, 0.19 mmol) in THF (2 mL) was added at 0 °C. After being stirred for 4 h, the reaction was quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **47** (14 mg, 21%) as light yellow oil. IR (film), 2935, 1607, 1523 and 1487 cm^{-1} ; δ_{H} (CDCl_3), 1.64 (3H, s), 1.72 (3H, s), 3.41 (2H, d, $J=5.7$ Hz), 3.86 (3H, s), 4.01 (3H, s), 4.92 (2H, s), 5.09 (1H, t, $J=5.7$ Hz), 6.20 (1H, s), 7.18-7.63 (5H, m)



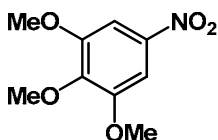
3-(Benzyloxy)-4,5-dimethoxy-2-(3-methylbut-2-enyl)aniline (**48**):

To a solution of **47** (14 mg, 0.040 mmol) in AcOH (2 mL) was added Zn powder. After being stirred for 40 min, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **48** (11 mg, 87%) as yellow oil. IR (film), 3439, 3365, 2930, 1604, 1496 and 1453 cm^{-1} ; δ_{H} (CDCl_3), 1.66 (3H, s), 1.72 (3H, s), 3.22 (2H, d, $J=6.8$ Hz), 3.78 (3H, s), 3.80 (3H, s), 4.92 (1H, t, $J=6.8$ Hz), 4.99 (2H, s), 6.07 (1H, s), 7.30-7.47 (5H, m)



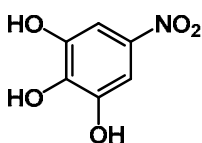
2-(3-(Benzyloxy)-4,5-dimethoxy-2-(3-methylbut-2-enyl)phenylamino)benzoic acid (49):

To a solution of **48** (11 mg, 0.034 mmol) in DMF (1.5 mL) were added 2-iodobenzoic acid (17 mg), KOAc (6.6 mg) and catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ at room temperature. After being stirred for 1.5 h at 90 °C, the reaction was cooled to room temperature, poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **49** (7.1 mg, 47%) as yellow oil. δ_{H} (CDCl_3), 1.49 (3H, s), 1.59 (3H, s), 3.22 (2H, d, $J=6.4$ Hz), 3.79 (3H, s), 3.90 (3H, s), 4.98 (1H, t, $J=6.4$ Hz), 5.06 (2H, s), 6.65-6.71 (3H, m), 7.25-7.47 (6H, m), 8.04 (1H, d, $J=8.0$ Hz), 8.87 (1H, br)



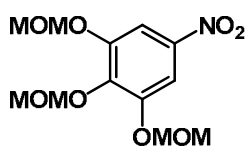
1,2,3-Trimethoxy-5-nitrobenzene (51):

To a solution of 3,4,5-trimethoxybenzoic acid (7.3 g, 0.34 mol) in CH_3CN (86 mL) were added HNO_3 (4.3 mL) and AIBN (0.11 g) at 0 °C. After being stirred for 15 h at 50 °C, the reaction mixture was poured into ice water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give **51** (5.5 g, 75%) as yellow needles. IR (KBr disk), 3111, 2979, 2838, 1619 and 1496 cm^{-1} ; mp 100-101 °C; δ_{H} (CDCl_3), 3.92 (9H, s), 7.50 (2H, s)



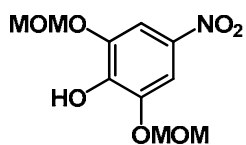
5-Nitrobenzene-1,2,3-triol (**52**):

To a solution of **51** (0.51 g, 2.4 mmol) in AcOH (10 mL) was added 47% HBr aq. (5 mL) at 0 °C. After being stirred for 1 d at 100 °C, the reaction mixture was poured into ice water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl₃/MeOH, 10/1) to give **52** (0.40 g, 99%) as light yellow needles. IR (KBr disk), 3429, 1616 and 1507 cm⁻¹; mp 195-196 °C; δ_H (acetone-d₆), 7.34 (2H, s), 8.79 (3H, br)



1,2,3-Tris(methoxymethoxy)-5-nitrobenzene (**53**):

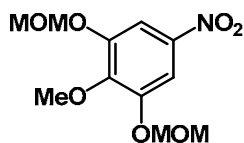
To a solution of **52** (0.51 g, 3.0 mmol) in CH₂Cl₂ (15 mL) were added *i*Pr₂NEt (0.79 mL) and MOMCl (3.6 mL) at 0 °C. After being stirred for 2.5 h at room temperature, the reaction was cooled to 0 °C and the reaction was quenched by the addition of sat. NH₄Cl aq. and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **53** (0.76 g, 85%) as light yellow needles. IR (KBr disk), 3430, 1616 and 1507 cm⁻¹; mp 209-210 °C; δ_H (CDCl₃), 3.49 (6H, s), 3.58 (3H, s), 5.22 (2H, s), 5.25 (4H, s), 7.75 (2H, s)



2,6-Bis(methoxymethoxy)-4-nitrophenol (**54**):

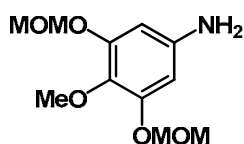
To a solution of **53** (0.14 g, 0.45 mmol) in MeOH (2 mL) was added 0.2M KOH aq. at 0 °C. After being stirred for 1 d at 80 °C, the reaction was cooled to 0 °C and quenched by 1M HCl and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/1) to give **54** (97 mg, 84%) as yellow oil. δ_H (CDCl₃), 3.53 (6H, s), 5.28 (3H, s), 6.42 (1H, br), 7.80 (2H, s);

δ_C (CDCl₃), 56.7, 95.9, 106.6, 142.7, 144.2



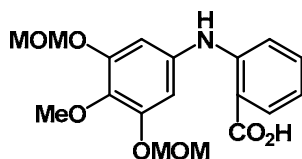
2-Methoxy-1,3-bis(methoxymethoxy)-5-nitrobenzene (55):

To a solution of **54** (97 mg, 0.37 mmol) in DMF (3 mL) were added MeI (0.070 mL) and K₂CO₃ (0.31 g) at 0 °C. After being stirred for 15 h at room temperature, the reaction was cooled to 0 °C and quenched by sat. NH₄Cl aq. Then the resulting slurry was extracted with Et₂O three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/2) to give **55** (97 mg, 95%) as light yellow needles. IR (KBr disk), 3126, 2948, 2835 and 1525 cm⁻¹; mp 78-79 °C; δ_H (CDCl₃), 3.51 (6H, s), 3.96 (3H, s), 5.26 (4H, s), 7.76 (2H, s); δ_C (CDCl₃), 56.6, 61.3, 95.3, 101.9, 106.1, 143.2, 145.4, 150.4



4-Methoxy-3,5-bis(methoxymethoxy)aniline (56):

To a solution of **55** (0.15 g, 0.56 mmol) in EtOH (2.5 mL) and H₂O (0.5 mL) were added Fe powder (0.31 g) and NH₄Cl (0.60 g) at room temperature. After being stirred for 1 h, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/CHCl₃, 1/40) to give **56** (0.14 g, quant.) as yellow oil. IR (film), 3447, 3365, 3232, 2954, 2826, 1609 and 1507 cm⁻¹; δ_H (CDCl₃), 3.48 (6H, s), 3.53 (2H, br), 3.76 (3H, s), 5.15 (4H, s), 6.19 (2H, s); δ_C (CDCl₃), 56.1, 61.2, 95.1, 97.5, 132.2, 142.8, 151.4



2-(4-Methoxy-3,5-bis(methoxymethoxy)phenylamino)benzoic acid (57):

To a solution of **56** (0.12 g, 0.48 mmol) in 2-propanol (2.5 mL) were added

2-iodobenzoic acid (0.24 g), KOAc (0.19 g), Et₃N (0.13 mL) and catalytic amounts of Cu(OAc)₂·H₂O at room temperature. After being stirred for 1 d at 90 °C, the reaction was cooled to room temperature, then the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by PTLC (EtOAc/hexane, 1/2) to give **57** (62 mg, 36%) as yellow needles. IR (KBr disk), 3347, 2956, 1659, 1599 and 1577 cm⁻¹; mp 126-127 °C; δ_H (CDCl₃), 3.51 (6H, s), 3.88 (3H, s), 5.20 (4H, s), 6.69 (1H, t, *J*=8.0 Hz), 6.77 (2H, s), 7.17 (1H, d, *J*=8.0 Hz), 7.32 (1H, td, *J*=8.0, 1.6 Hz), 8.00 (1H, dd, *J*=8.0, 1.6 Hz), 9.18 (1H, br); δ_C (CDCl₃), 56.2, 61.2, 95.2, 106.2, 110.2, 114.0, 116.9, 132.4, 135.0, 136.1, 136.7, 148.9, 151.2, 173.3



(5-Nitrobenzene-1,2,3-triyl)tris(oxy)tris(methylene)tribenzene (58):

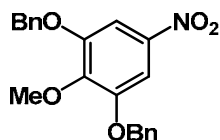
To a solution of **52** (0.17 g, 1.0 mmol) in DMF (2 mL) were added BnBr (0.36 mL) and K₂CO₃ (0.98 g) at 0 °C. After being stirred for 32 h at room temperature, the reaction was cooled to 0 °C and the reaction was quenched by sat. NH₄Cl aq. and the resulting slurry was extracted with Et₂O three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give **58** (0.25 g, 57%) as yellow needles. IR (KBr disk), 3110, 3030, 1621 and 1520 cm⁻¹; mp 144-145 °C; δ_H (CDCl₃), 5.14 (6H, s), 7.26-7.40 (15H, m), 7.56 (2H, s)



2,6-Bis(benzyloxy)-4-nitrophenol (59):

To a solution of **58** (0.51 g, 1.2 mmol) in DMSO (6 mL) was added 10M KOH aq. at room temperature. After being stirred for 1 d at 70 °C, the reaction was cooled to room temperature, quenched by 3M HCl and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The

residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **59** (0.38 g, 93%) as yellow oil. δ_{H} (CDCl_3), 5.19 (4H, s), 6.14 (1H, br), 7.33-7.46 (10H, m), 7.61 (2H, s)



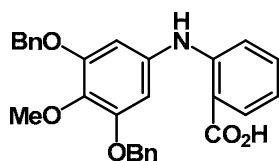
(2-Methoxy-5-nitro-1,3-phenylene)bis(oxy)bis(methylene)dibenzene (60):

To a solution of **59** (0.38 g, 1.1 mmol) in DMF (5 mL) were added MeI (0.13 mL) and K_2CO_3 (0.59 g) at 0 °C. After being stirred for 14 h at room temperature, the reaction was cooled to 0 °C and the reaction was quenched by sat. NH_4Cl aq. and the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **60** (0.34 g, 88%) as light yellow needles. IR (KBr disk), 3096, 2942, 1615 and 1515 cm^{-1} ; mp 134-135 °C; δ_{H} (CDCl_3), 3.97 (3H, s), 5.17 (4H, s), 7.33-7.47 (10H, m), 7.57 (2H, s); δ_{C} (CDCl_3), 61.2, 71.3, 103.3, 127.3, 128.2, 128.6, 135.6, 142.9, 144.8, 151.8



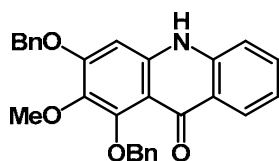
3,5-Bis(benzyloxy)-4-methoxyaniline (61):

To a solution of **60** (0.19 g, 0.52 mmol) in EtOH (2.5 mL) and H_2O (0.5 mL) were added Fe powder (0.29 g) and NH_4Cl (0.56 g) at room temperature. After being stirred for 2.5 h at 70 °C, the reaction was cooled to room temperature, then filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **61** (0.16 g, 93%) as yellow needles. IR (KBr disk), 3434, 3347, 2925, 1593 and 1507 cm^{-1} ; mp 135-136 °C; δ_{H} (CDCl_3), 3.45 (2H, br), 3.82 (3H, s), 5.08 (4H, s), 5.95 (2H, s), 7.26-7.44 (10H, m); δ_{C} (CDCl_3), 61.2, 70.9, 95.4, 127.0, 127.6, 128.4, 137.2, 142.5, 153.0



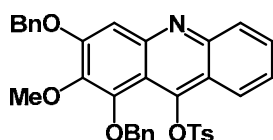
2-(3,5-Bis(benzyloxy)-4-methoxyphenylamino)benzoic acid (**62**):

To a solution of **61** (0.20 g, 0.60 mmol) in DMF (3 mL) were added 2-iodobenzoic acid (0.22 g), KOAc (0.18 g) and catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ at room temperature. After being stirred for 3.5 h at 90 °C, the reaction was cooled to room temperature, then poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane 1/1) to give **62** (0.22 g, 80%) as light yellow needles. IR (KBr disk), 3345, 2877, 1669 and 1572 cm^{-1} ; mp 165-166 °C; δ_{H} (CDCl_3), 3.92 (3H, s), 5.12 (4H, s), 6.50 (2H, s), 6.71 (1H, t, $J=8.0$ Hz), 6.83 (1H, d, $J=8.0$ Hz), 7.20 (1H, t, $J=8.0$ Hz), 7.30-7.44 (10H, m), 8.00 (1H, d, $J=8.0$ Hz), 9.15 (1H, br); δ_{C} (CDCl_3), 61.1, 71.0, 103.6, 110.0, 113.9, 116.9, 127.2, 127.8, 128.5, 132.4, 135.2, 135.7, 136.2, 136.8, 148.9, 152.7, 173.3



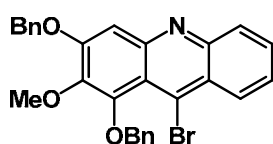
1,3-Bis(benzyloxy)-2-methoxyacridin-9(10H)-one (**64**):

To a solution of **62** (0.13 g, 0.29 mmol) in CH_2Cl_2 (1.5 mL) was added TFAA (0.40 mL) at room temperature. After being stirred for 11 d, the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/ CHCl_3 , 50/1) to give **64** (0.12 g, 91%) as light yellow powder. IR (KBr disk), 2932, 1635, 1597 and 1550 cm^{-1} ; mp 201-202 °C; δ_{H} (CDCl_3), 3.79 (3H, s), 4.83 (2H, s), 5.20 (2H, s), 6.94 (1H, s), 7.05-7.28 (9H, m), 7.49 (3H, m), 7.58 (1H, d, $J=8.0$ Hz), 8.38 (1H, d, $J=8.0$ Hz), 11.79 (1H, br)



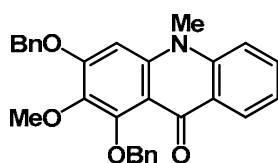
1,3-Bis(benzyloxy)-2-methoxyacridin-9-yl 4-methylbenzenesulfonate (**65**)

To a solution of **64** (6.1 mg, 0.014 mmol) in DMF (1.0 mL) were added NaH (60% dispersion in mineral oil) and MeI (10 μ L) at 0 $^{\circ}$ C. After being stirred for 14 h at room temperature, the reaction was quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by PTLC (EtOAc/hexane, 1/2) to give **65** (4.0 mg, 48%) as yellow oil. δ_{H} (CDCl₃), 2.34 (3H, s), 3.88 (3H, s), 4.90 (2H, s), 5.30 (2H, s), 7.03 (2H, d, $J=8.3$ Hz), 7.33-7.53 (14H, m), 7.70 (1H, t, $J=6.8$ Hz), 7.99 (1H, d, $J=9.3$ Hz), 8.06 (1H, d, $J=8.8$ Hz)



1,3-Bis(benzyloxy)-9-bromo-2-methoxyacridine (66):

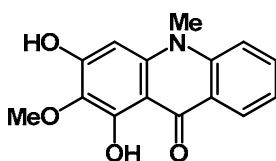
To a solution of **65** (3.9 mg, 0.0065 mmol) in benzene (1.4 mL) and Et₂O (0.2 mL) was added MgBr₂·Et₂O at room temperature. After being stirred for 1 h at 70 $^{\circ}$ C, the reaction was cooled to room temperature, then poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by PTLC (EtOAc/hexane 1/2) to give **66** (2.4 mg, 74%) as yellow oil. δ_{H} (CDCl₃), 4.01 (3H, s), 5.20 (2H, s), 5.31 (2H, s), 7.35-7.65 (12H, m), 7.73 (1H, t, $J=8.0$ Hz), 8.06 (1H, d, $J=8.0$ Hz), 8.56 (1H, d, $J=8.8$ Hz)



1,3-Bis(benzyloxy)-2-methoxy-10-methylacridin-9(10H)-one (67):

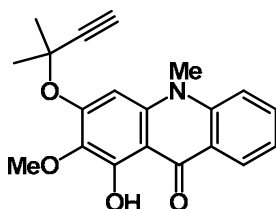
To a solution of **66** (0.12 g, 0.27 mmol) in THF (1.5 mL) were added NaH (0.016 g, 60% dispersion in mineral oil) and MeI (0.020 mL) at 0 $^{\circ}$ C. After being stirred for 4 h at room temperature, the reaction was quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **67** (98 mg, 82%) as orange powder.

IR (KBr disk), 2933, 1597 and 1496 cm^{-1} ; mp 156-157 ; δ_{H} (CDCl_3), 3.61 (3H, s), 3.87 (3H, s), 5.20 (2H, s), 5.23 (2H, s), 6.60 (1H, s), 7.18 (1H, t, $J=7.2$ Hz), 7.28-7.47 (9H, m), 7.55 (1H, td, $J=7.2, 1.2$ Hz), 7.73-7.75 (2H, m), 8.48 (1H, dd, $J=7.2, 1.2$ Hz); δ_{C} (CDCl_3), 34.5, 61.4, 70.8, 76.1, 94.9, 112.5, 114.1, 120.9, 123.6, 127.1, 127.4, 127.6, 128.1, 128.6, 128.7, 132.6, 136.0, 137.7, 138.3, 141.4, 141.6, 153.3, 156.6, 176.2



1,3-Dihydroxy-2-methoxy-10-methylacridin-9(10H)-one (**68**)

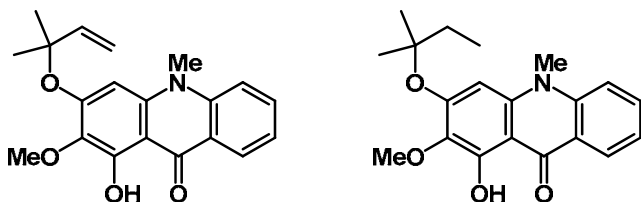
To a solution of **67** (0.10 g, 0.23 mmol) in MeOH (2 mL) was added 10% Pd-C at room temperature. After being stirred for 13 h under H_2 atmosphere, the resulting slurry was filtered through a celite pad. The filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (MeOH/ CHCl_3 , 1/50) to give **68** (19 mg, 32%) as yellow oil. IR (film), 3339, 2925, 1645 and 1598 cm^{-1} ; δ_{H} (CDCl_3), 3.80 (3H, s), 4.03 (3H, s), 6.46 (1H, s), 6.54 (1H, br), 7.29 (1H, t, $J=8.0$ Hz), 7.49 (1H, d, $J=8.8$ Hz), 7.72 (1H, t, $J=8.8$ Hz), 8.46 (1H, d, $J=8.0$ Hz), 15.10 (1H, s)



1-Hydroxy-2-methoxy-10-methyl-3-(2-methylbut-3-yn-2-yloxy)acridin-9(10H)-one(**69**):

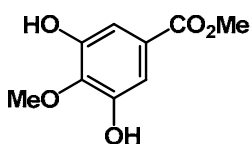
To a solution of **68** (19 mg, 0.071 mmol) in DMF (1 mL) were added K_2CO_3 (20 mg), KI (24 mg) and 3-chloro-3-methyl-1-butyne (64 μL) at room temperature. After being stirred for 1 d at 65 , the reaction was cooled to room temperature and poured into water, then the resulting slurry was extracted with CHCl_3 three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **69** (12 mg, 48%) as yellow oil. δ_{H} (CDCl_3), 1.78 (6H, s), 2.72 (1H, s), 3.78 (3H, s), 3.87 (3H, s),

7.14 (1H, s), 7.26 (1H, t, $J=8.8$ Hz), 7.46 (1H, d, $J=8.8$ Hz), 7.70 (1H, td, 8.0, 1.6 Hz), 8.41 (1H, dd, $J=8.0, 1.6$ Hz), 14.63 (1H, s)



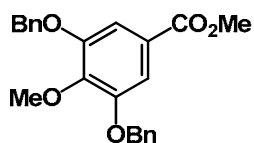
1-Hydroxy-2-methoxy-10-methyl-3-(2-methylbut-3-en-2-yloxy)acridin-9(10H)-one (70), 1-hydroxy-2-methoxy-10-methyl-3-(tert-pentyloxy)acridin-9(10H)-one (71):

To a solution of **69** (6.7 mg, 0.020 mmol) in MeOH (1 mL) were added quinoline (50 μ L) and Lindlar catalyst at room temperature. After being stirred for 2 h under H₂ atmosphere, the resulting slurry was filtered through a celite pad. The filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **70** (1.6 mg, 24%) as yellow oil and **71** (3.7 mg, 55%) as yellow oil. **70**: IR (film) 3481, 3087, 1645 and 1594 cm^{-1} ; δ_{H} (CDCl₃), 1.58 (6H, s), 3.90 (6H, s), 4.15 (1H, d, $J=18.1$ Hz), 5.52 (1H, d, $J=9.5$ Hz), 5.57 (1H, d, $J=9.5$ Hz), 7.24 (1H, s), 7.30 (1H, t, $J=8.6$ Hz), 7.42 (1H, d, $J=8.6$ Hz), 7.72 (1H, t, $J=8.6$ Hz), 8.38 (1H, d, $J=8.6$ Hz), 14.83 (1H, s)



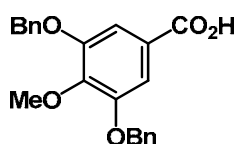
Methyl 3,5-dihydroxy-4-methoxybenzoate (72):

To a solution of methylgallate (2.1 g, 11 mmol) in DMF (56 mL) were added Li₂CO₃ (2.1 g) and MeI (1.7 mL) at 0 °C. After being stirred for 20 h at 55 °C, the reaction was cooled to room temperature and quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/CHCl₃, 1/50) to give **72** (1.3 g, 57%) as colorless needles. IR (KBr disk), 3387, 1710, 1597 and 1508 cm^{-1} ; mp 152-153 °C; δ_{H} (CDCl₃), 3.75 (3H, s), 3.86 (3H, s), 7.09 (2H, s)



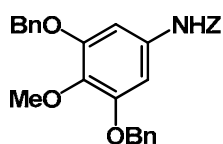
Methyl 3,5-bis(benzyloxy)-4-methoxybenzoate (**73**):

To a solution of **72** (1.5 g, 7.7 mmol) in acetone (15 mL) were added K_2CO_3 (5.3 g) and BnBr (1.8 mL) at 0 °C. After being stirred for 20 h at room temperature, the reaction was quenched by the addition of water and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give **73** (2.8 g, 95%) as colorless prism. IR (KBr disk), 3028, 1707 and 1588 cm^{-1} ; mp 126-127 °C; δ_H ($CDCl_3$), 3.86 (3H, s), 3.92 (3H, s), 5.14 (4H, s), 7.31-7.45 (12H, m); δ_C ($CDCl_3$), 52.3, 61.0, 71.2, 109.1, 124.9, 127.3, 127.9, 128.5, 136.6, 143.5, 152.1, 166.5



3,5-Bis(benzyloxy)-4-methoxybenzoic acid (**74**):

To a solution of **73** (0.51 g, 1.4 mmol) in THF (3 mL) was added 20% NaOH aq. at 0 °C. After being stirred for 12 h at 70 °C, the reaction mixture was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from MeOH to give **74** (0.45 g, 91%) as colorless needles. IR (KBr disk), 2938, 2634, 1679 and 1583 cm^{-1} ; mp 171-172 °C; δ_H (CD_3OD), 3.80 (3H, s), 5.06 (2H, s), 5.08 (2H, s), 7.01 (1H, s), 7.29-7.50 (10H, m); δ_C (CD_3OD), 60.9, 61.6, 62.4, 63.0, 72.3, 76.6, 87.9, 109.9, 121.9, 127.7, 128.0, 128.5, 128.7, 129.1, 129.2, 129.4, 130.1, 138.5, 139.0, 145.5, 147.0, 149.3, 181.6, 181.7



Benzyl 3,5-bis(benzyloxy)-4-methoxyphenylcarbamate (**75**):

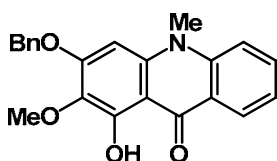
To a solution of **74** (0.45 g, 1.2 mmol) in toluene (6 mL) were added DPPA (0.28 mL), Et_3N (0.18 mL) and BnOH (0.14 mL) at room temperature. After being stirred for 15 h at 80 °C, the solvent was removed *in vacuo* and the residue was

purified by silica gel column chromatography (EtOAc/hexane, 1/6) to give **75** (0.65 g, include BnOH) as colorless oil. IR (film), 3032, 2942, 1729 and 1606 cm^{-1} ; δ_{H} (CDCl_3), 3.84 (3H, s), 5.08 (4H, m), 5.16 (2H, s), 6.70 (1H, br), 6.72 (2H, s), 7.29-7.44 (15, m)



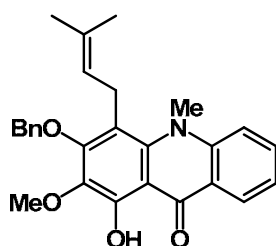
3,5-Bis(benzyloxy)-4-methoxyaniline (**61**):

To a solution of **75** (0.58 g, 1.2 mmol) in MeOH (6 mL) was added 40% KOH aq. at 0 . After being stirred for 4 h at 80 . Then the reaction mixture was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give **61** (0.37 g, 90%) as colorless crystals. Spectrum details are same as made from **60**.



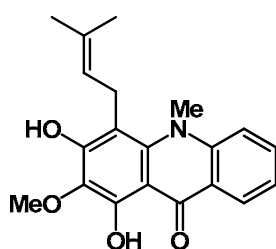
3-(Benzyloxy)-1-hydroxy-2-methoxy-10-methylacridin-9(10H)-one (**76**):

To a solution of **67** (0.13 g, 0.28 mmol) in benzene (2.8 mL) and Et_2O (0.4 mL) was added $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (87 mg) at room temperature. After being stirred for 10 h under reflux, the reaction was cooled to room temperature and poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($\text{CHCl}_3/\text{MeOH}$, 50/1) to give **76** (94 mg, 97%) as yellow needles. IR (KBr disk), 2935, 1635 and 1593 cm^{-1} ; mp 212-213 ; δ_{H} (CDCl_3), 3.62 (3H, s), 3.91 (3H, s), 5.21 (2H, s), 6.17 (1H, s), 7.12-7.64 (8H, m), 8.25 (1H, d, $J=7.6$ Hz), 14.72 (1H, s); δ_{C} (CDCl_3), 29.8, 34.0, 60.8, 70.7, 88.6, 105.6, 114.4, 120.3, 121.2, 126.2, 127.1, 128.1, 128.6, 133.7, 136.1, 139.9, 141.6, 156.0, 158.1, 180.4; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_4$ (M+H) 362.1387, found: m/z 362.1387



3-(Benzyloxy)-1-hydroxy-2-methoxy-10-methyl-4-(3-methylbut-2-enyl)acridin-9(10H)-one (78):

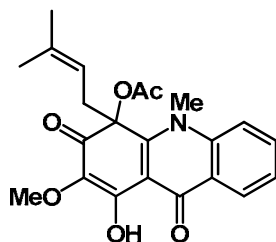
To a solution of **76** (61 mg, 0.17 mmol) in THF (2 mL) were added NaH (21 mg, 60% dispersion in mineral oil) and prenyl bromide (0.1 mL) at 0 °C. After being stirred for 3.5 h at 50 °C, the reaction was quenched by the addition of water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was spreading to silica gel for 15 h, then purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **78** (30 mg, 40%) as orange solid. IR (KBr disk), 2916, 1628 and 1583 cm⁻¹; δ_H (CDCl₃), 1.65 (3H, s), 1.69 (3H, s), 3.41 (2H, d, *J*=4.4 Hz), 3.79 (3H, s), 3.93 (3H, s), 5.26 (3H, m), 7.26-7.45 (7H, m), 7.69 (1H, t, *J*=7.2 Hz), 8.35 (1H, d, *J*=7.2 Hz), 14.64 (1H, s); δ_C (CDCl₃), 18.1, 25.6, 27.7, 43.8, 60.7, 75.2, 109.4, 112.3, 116.3, 121.1, 121.4, 124.2, 126.0, 127.88, 127.9, 128.3, 131.9, 134.0, 134.5, 137.4, 142.5, 145.9, 154.9, 158.2, 182.3; HRMS (FAB) calcd for C₂₇H₂₇NO₄ (M) 429.1940, found: *m/z* 429.1934



1,3-Dihydroxy-2-methoxy-10-methyl-4-(3-methylbut-2-enyl)acridin-9(10H)-one (17):

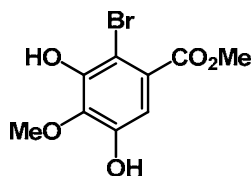
To a solution of **78** (25 mg, 0.059 mmol) in MeOH (1 mL) were added excess amounts of 1,4-cyclohexadiene and cat. Pd black. After being stirred for 2 h, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **17** (14 mg, 72%) as yellow powder. IR (film), 3273,

1616 and 1594 cm^{-1} ; δ_{H} (CDCl_3), 1.75 (3H, s), 1.76 (3H, s), 3.48 (2H, d, $J=4.9$ Hz), 3.83 (3H, s), 4.03 (3H, s), 5.36 (1H, t, $J=4.9$ Hz), 6.75 (1H, s), 7.25 (1H, t, $J=8.8$ Hz), 7.39 (1H, d, $J=8.8$ Hz), 7.68 (1H, t, $J=7.8$ Hz), 8.34 (1H, d, $J=7.8$ Hz), 14.94 (1H, s); δ_{C} (CDCl_3), 18.2, 25.7, 27.2, 43.6, 60.8, 104.5, 107.1, 116.2, 121.0, 121.4, 123.5, 125.9, 128.3, 132.5, 133.7, 143.0, 145.5, 152.8, 155.3, 182.0; HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_4$ ($\text{M}+\text{H}$) 340.1543, found: m/z 340.1569



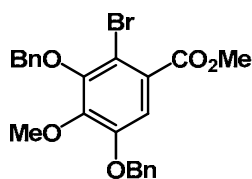
1-Hydroxy-2-methoxy-10-methyl-4-(3-methylbut-2-enyl)-3,9-dioxo-3,4,9,10-tetrahydroacridin-4-yl acetate (79):

To a solution of **17** (4.5 mg, 0.013 mmol) in benzene (1 mL) was added $\text{Pb}(\text{OAc})_4$ (7.1 mg) at room temperature. After being stirred for 1 h, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone/toluene, 1/10) to give **79** (3.9 mg, 74%) as orange oil.



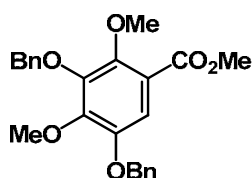
Methyl 2-bromo-3,5-dihydroxy-4-methoxybenzoate (80):

To a solution of **72** (0.61 g, 3.1 mmol) in CHCl_3 (15 mL) was added DBDMH (0.44 g) portion wise. After being stirred for 15 h, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give mixture of **72**, **80** and dibromo **80** as colorless solid.



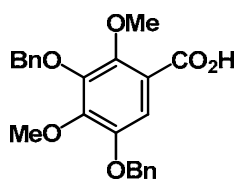
Methyl 3,5-bis(benzyloxy)-2-bromo-4-methoxybenzoate (**81**):

To a solution of **72**, **80** and dibromo **80** mixture in DMF (15 mL) were added K_2CO_3 (2.1 g) and BnBr (0.73 mL) at 0 °C. After being stirred for 14 h, the reaction was quenched by the addition of water and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give mixture of **81** and dibromo **73** (0.88 g) as colorless solid.



Methyl 3,5-bis(benzyloxy)-2,4-dimethoxybenzoate (**82**):

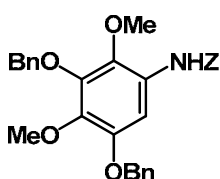
To a solution of Na (0.21 g) in MeOH (5 mL) was added **81** and dibromo **73** mixture (1.5 g) in DMF (5 mL) and CuI (1.3 g) at 0 °C. After being stirred for 5 h at 100 °C, the reaction was quenched by the addition of 2M HCl and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone/toluene, 1/5) to give **82** (0.74 g, 38% in 3 steps) as colorless oil. IR (film), 2939, 1729 and 1594 cm^{-1} ; δ_H ($CDCl_3$), 3.89 (6H, s), 3.91 (3H, s), 5.06 (2H, s), 5.09 (2H, s), 7.25 (1H, s), 7.32-7.52 (10H, m); δ_C ($CDCl_3$), 52.2, 61.3, 62.1, 71.3, 75.7, 110.9, 119.1, 127.4, 127.9, 128.0, 128.2, 128.3, 128.5, 136.5, 137.2, 146.7, 147.8, 148.1, 149.3, 165.9



3,5-Bis(benzyloxy)-2,4-dimethoxybenzoic acid (**83**):

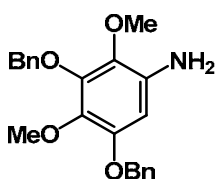
To a solution of **82** (0.64 g, 1.6 mmol) in MeOH (8 mL) was added 20% NaOH aq.

(2.5 mL) at 0 °C. After being stirred for 2 h at 75 °C, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was recrystallized from MeOH to give **83** (0.54 g, 88%) as colorless solid. IR (KBr disk), 3447, 2938, 1608, 1587 and 1564 cm⁻¹; δ_H (CD₃OD), 3.80 (3H, s), 3.84 (3H, s), 5.06 (2H, s), 5.08 (2H, s), 7.01 (1H, s), 7.29-7.50 (10H, m); δ_C (CD₃OD), 60.9, 61.6, 62.4, 63.0, 72.3, 76.6, 87.9, 109.9, 121.9, 127.7, 128.0, 128.5, 128.7, 129.1, 129.2, 129.4, 130.1, 138.5, 139.0, 145.5, 147.0, 149.3, 181.6



Benzyl 3,5-bis(benzyloxy)-2,4-dimethoxyphenylcarbamate (84):

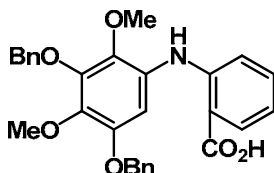
To a solution of **83** (0.52 g, 1.3 mmol) in toluene (13 mL) were added DPPA (0.30 mL), Et₃N (0.19 mL) and BnOH (0.15 mL) at room temperature. After being stirred for 6.5 h at 80 °C, the solvent was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **84** (0.53 g, 81%) as colorless oil. IR (film), 3420, 3328, 2936, 2143, 1733, 1603 and 1520 cm⁻¹; δ_H (CDCl₃), 3.81 (3H, s), 3.83 (3H, s), 5.08 (4H, m), 5.20 (2H, s), 7.29-7.50 (16H, m), 7.72 (1H, m); δ_C (CDCl₃), 61.3, 61.4, 67.0, 71.1, 75.58, 75.6, 99.8, 127.0, 127.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.37, 128.4, 128.6, 135.9, 136.0, 136.9, 137.4, 138.8, 145.4, 148.5, 153.2, 180.22, 180.23



3,5-Bis(benzyloxy)-2,4-dimethoxyaniline (85):

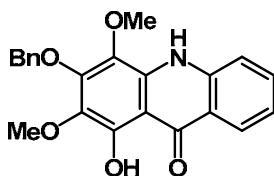
To a solution of **84** (0.49 g, 0.99 mmol) in MeOH (6 mL) was added 40% KOH aq. (2 mL) at 0 °C. After being stirred for 12 h at 75 °C, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/2) to give **85** (0.32 g, 89%) as pale purple

crystals. IR (KBr disk), 3468, 3363, 2935, 1613 and 1502 cm^{-1} ; mp 118-119 ; δ_{H} (CDCl_3), 3.82 (3H, s), 3.94 (2H, br), 5.06 (4H, s), 6.21 (1H, s), 7.31-7.56 (10H, m); δ_{C} (CDCl_3), 19.8, 60.7, 61.5, 71.3, 75.4, 97.6, 127.1, 127.7, 127.8, 128.0, 128.3, 128.4, 134.9, 135.6, 137.2, 137.8, 148.8



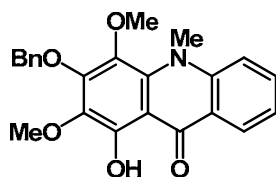
2-(3,5-Bis(benzyloxy)-2,4-dimethoxyphenylamino)benzoic acid (**85**):

To a solution of **85** (0.18 g, 0.49 mmol) in DMF (2.5 mL) were added 2-iodobenzoic acid (0.14 g), KOAc (0.11 g) and catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ at room temperature. After being stirred for 14 h at 90 , the reaction was cooled to room temperature, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/ CHCl_3 , 1/30) to give mixture of **86** and inseparable other high-polar compounds.



3-(Benzyloxy)-1-hydroxy-2,4-dimethoxyacridin-9(10H)-one (**87**):

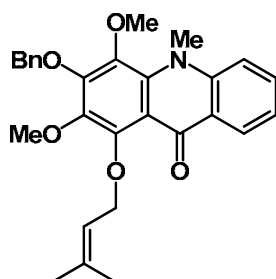
To a solution of **86** and inseparable other high-polar compounds mixture in CH_2Cl_2 (2.4 mL) was added TFAA (0.68 mL) at room temperature. After being stirred for 10 d, the solvent was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/8) to give **87** (0.13 g, 73% in 2 steps) as orange powder. IR (KBr disk), 2949, 1765 and 1596 cm^{-1} ; mp 142-143 ; δ_{H} (CDCl_3), 3.61 (3H, s), 3.94 (3H, s), 5.37 (2H, s), 7.32-7.50 (7H, m), 7.71 (1H, td, $J=8.0, 1.6$ Hz), 8.44 (1H, dd, $J=8.0, 1.6$ Hz), 13.41 (1H, s); δ_{C} (CDCl_3), 60.8, 61.1, 75.9, 105.2, 114.3, 117.2, 120.5, 124.0, 127.2, 127.8, 128.4, 128.5, 130.2, 130.9, 135.0, 136.1, 136.3, 138.0, 151.1, 153.0, 159.8, 160.3, 181.9; HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_5$ (M+H) 378.1336, found: m/z 378.1325



3-(Benzyloxy)-1-hydroxy-2,4-dimethoxy-10-methylacridin-9(10H)-one (**88**):

To a solution of **87** (51 mg, 0.13 mmol) in MeCN (1.5 mL) were added 35% HCHO (0.23 mL) and NaCNBH₃ at 0 °C. After being stirred for 30 min, AcOH was added to reaction mixture until acidic condition at 0 °C. After being stirred for 12 h, the reaction was quenched by the addition of 2M NaOH aq. and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/3) to give **pre-88** (42 mg, 83%) as yellow solid.

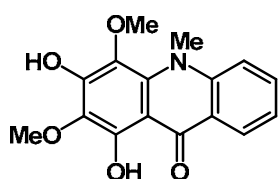
To a solution of **pre-88** (42 mg, 0.11 mmol) in acetone (1.5 mL) were added K₂CO₃ (76 mg) and MeI (14 μL) at 0 °C. After being stirred for 20 h, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/7) to give **88** (30 mg, 70%) as orange needles. IR (KBr disk), 2949, 1765, 1645 and 1596 cm⁻¹; mp 143-144 °C; δ_H (CDCl₃), 3.71 (3H, s), 3.93 (3H, s), 4.02 (3H, s), 5.34 (2H, s), 7.24-7.56 (7H, m), 7.72(1H, td, *J* = 8.0, 1.6 Hz), 8.40 (1H, dd, *J* = 8.0, 1.6 Hz), 14.50 (1H, s); δ_C (CDCl₃), 40.6, 61.0, 61.9, 75.8, 108.0, 115.5, 120.8, 121.4, 126.2, 128.1, 128.4, 133.3, 134.1, 134.5, 134.9, 137.2, 144.9, 152.7, 153.3, 180.22, 180.23, 182.0



3-(Benzyloxy)-2,4-dimethoxy-10-methyl-1-(3-methylbut-2-enyloxy)acridin-9(10H)-one (**89**):

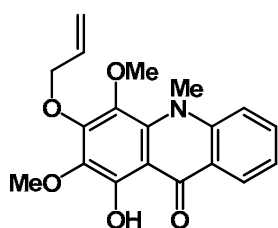
To a solution of **88** (9.3 mg, 0.024 mmol) in DMF (1 mL) were added K₂CO₃ (0.16

g) and prenyl bromide (69 μL) at 0 $^{\circ}\text{C}$. After being stirred for 5 h, the reaction was poured into water and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($\text{EtOAc}/\text{hexane}$, 1/20 to 1/5) to give **89** (7.7 mg, 70%) as orange oil. δ_{H} (CDCl_3), 1.71 (3H, s), 1.73 (3H, s), 3.68 (3H, s), 3.82 (3H, s), 3.84 (3H, s), 4.56 (2H, d, $J=7.2$ Hz), 5.22 (2H, s), 5.72 (1H, t, $J=7.2$ Hz), 7.14 (1H, t, $J=7.2$ Hz), 7.19-7.34 (6H, m), 7.56 (1H, t, $J=7.2$ Hz), 8.29 (1H, d, $J=7.2$ Hz)



1,3-Dihydroxy-2,4-dimethoxy-10-methylacridin-9(10H)-one (**92**):

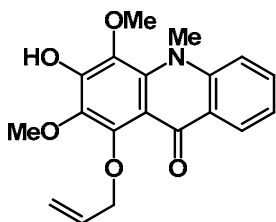
To a solution of **88** (29 mg, 0.074 mmol) in MeOH (1 mL) were added excess amounts of 1,4-cyclohexadiene and cat. Pd black. After being stirred for 3 h, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($\text{EtOAc}/\text{hexane}$, 1/2) to give **92** (21 mg, 93%) as yellow oil. IR (film), 3336, 2931 and 1616 cm^{-1} ; δ_{H} (CDCl_3), 3.78 (3H, s), 4.06 (3H, s), 4.07 (3H, s), 6.49 (1H, s), 7.30 (1H, s), 7.49 (1H, s), 7.34 (1H, s), 8.40 (1H, s), 14.80 (1H, s); δ_{C} (CDCl_3), 39.9, 60.9, 61.6, 105.5, 115.3, 120.8, 121.5, 126.2, 127.0, 128.1, 128.4, 128.5, 133.9, 134.7, 144.6, 150.3, 151.8, 181.7



3-(Allyloxy)-1-hydroxy-2,4-dimethoxy-10-methylacridin-9(10H)-one (**93**):

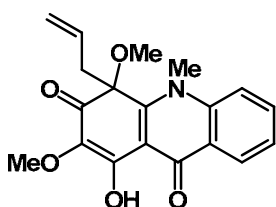
To a solution of **92** (1.5 mg, 0.0050 mmol) in acetone (1 mL) were added K_2CO_3 (32 mg) and allyl bromide (10 μL) at 0 $^{\circ}\text{C}$. After being stirred for 1.5 h, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by

silica gel column chromatography (EtOAc/hexane, 1/5) to give **93** (1.1 mg, 65%) as orange oil. δ_{H} (CDCl₃), 3.75 (3H, s), 3.96 (3H, s), 4.03 (3H, s), 4.84 (2H, d, J =5.7 Hz), 5.29 (1H, d, J =11.6 Hz), 5.47 (1H, dd, J =17.3, 1.6 Hz), 6.08-6.22 (1H, m), 7.29 (1H, t, J =8.4 Hz), 7.60 (1H, d, J =8.4 Hz), 7.73 (1H, td, J =6.8, 1.6 Hz), 8.40 (1H, dd, J =6.8, 1.6 Hz), 14.48 (1H, s)



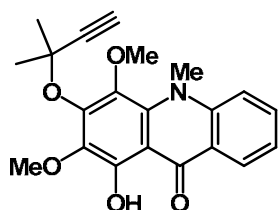
4-Allyl-1-hydroxy-2,4-dimethoxy-10-methylacridine-3,9(4H,10H)-dione (94):

To a solution of **93** in CH₂Cl₂ was added BF₃·Et₂O at -60 °C. After being stirred for 2 h, the reaction was poured into water and the resulting slurry was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by PTLC (EtOAc/hexane, 1/1) to give **94** as yellow oil. δ_{H} (CDCl₃), 3.83 (3H, s), 4.07 (3H, s), 4.35 (3H, s), 4.94 (2H, d, J =5.2 Hz), 5.31 (1H, d, J =10.4 Hz), 5.47 (1H, d, 16.8 Hz), 6.13 (1H, m), 7.52 (1H, t, J =8.8 Hz), 7.74 (1H, d, J =8.8 Hz), 7.96 (1H, t, J =8.0 Hz), 6.65 (1H, d, J =8.0 Hz)



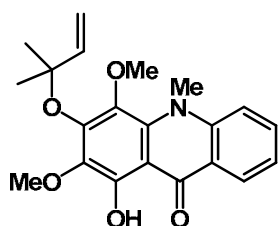
4-Allyl-1-hydroxy-2,4-dimethoxy-10-methylacridine-3,9(4H,10H)-dione (95):

93 was heated at 200 °C without solvent for 30 min. After being cooled to room temperature, the reaction mixture was purified by PTLC (MeOH/CHCl₃, 1/20) to give **95** as orange oil. δ_{H} (CDCl₃), 2.93 (1H, dd, J =6.8, 13.5 Hz), 3.11 (1H, dd, J =6.8, 13.5 Hz), 3.21 (3H, s), 3.85 (3H, s), 4.48 (3H, s), 4.90-4.97 (2H, m), 5.42-5.52 (1H, m), 7.63 (1H, t, J =7.0 Hz), 7.81-7.93 (2H, m), 8.54 (1H, d, J =8.1 Hz)



1-Hydroxy-2,4-dimethoxy-10-methyl-3-(2-methylbut-3-yn-2-yloxy)acridin-9(10H)-one (96):

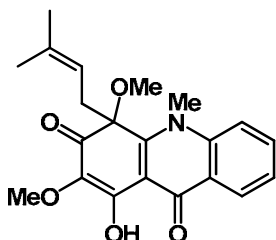
To a solution of **92** (20 mg, 0.065 mmol) in acetone (2 mL) were added K_2CO_3 (18 mg), KI (22 mg), CuI (25 mg) and 3-chloro-3-methyl-1-butyne (0.15 mL) at 0 °C. After being stirred for 3 h at room temperature, the reaction was poured into water and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **96** (18 mg, 75%) as orange prism. IR (KBr disk), 3250, 2932, 2562 and 1627 cm^{-1} ; mp 146-147 °C; δ_H ($CDCl_3$), 1.82 (6H, s), 2.46(1H, s), 3.74 (3H, s), 3.96 (3H, s), 4.05 (3H, s), 7.27 (1H, t, $J=8.0$ Hz), 7.49 (1H, d, $J=8.0$ Hz), 7.73 (1H, t, $J=8.0$ Hz), 8.39 (1H, d, $J=8.0$ Hz), 14.37 (1H, s); δ_C ($CDCl_3$), 30.3, 40.8, 60.6, 61.3, 73.2, 76.7, 77.9, 85.5, 108.9, 115.5, 120.9, 121.3, 126.3, 128.1, 128.4, 134.2, 144.9, 150.7, 152.2, 180.2, 182.2; HRMS (FAB) calcd for $C_{21}H_{21}NO_5$ (M) 367.1420, found: m/z 367.1438



1-Hydroxy-2,4-dimethoxy-10-methyl-3-(2-methylbut-3-en-2-yloxy)acridin-9(10H)-one (98):

To a solution of **96** (4.4 mg, 0.012 mmol) in benzene (0.5 mL) and hexane (2.5 mL) were added Lindlar catalyst and quinoline (20 μ L) at room temperature. After being stirred for 5 min under H_2 atmosphere, the reaction was filtrated by celite pad and the filtration was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane/toluene, 1/10/10) to give **96** (1.8 mg, 41%) and **92** (1.0 mg, 28%). δ_H ($CDCl_3$), 1.59 (6H, s), 3.70 (3H, s), 3.91 (3H, s), 4.01 (3H, s), 5.15 (1H, dd, $J=10.8, 1.0$ Hz), 5.22 (1H, dd, J

=17.4, 1.0 Hz), 6.30 (1H, dd, $J=10.8, 17.4$ Hz), 7.28 (1H, t, $J=8.8$ Hz), 7.48 (1H, d, $J=8.8$ Hz), 7.73 (1H, td, $J=8.8, 1.6$ Hz), 8.39 (1H, dd, $J=8.8, 1.6$ Hz), 14.33 (1H, s); δ_C (CDCl₃), 9.2, 25.7, 26.7, 35.5, 40.9, 60.36, 60.40, 61.1, 113.0, 115.6, 121.4, 126.4, 134.2, 134.8, 137.0, 143.3, 145.1, 151.3, 152.5, 182.2



Megistophylline :

97 (3.1 mg, 0.0084 mmol) was heated at 200 without solvent for 30 min. After being cooled to room temperature, the reaction mixture was purified by PTLC (MeOH/CHCl₃, 1/20) to give **megistophylline** (2.0 mg, 65%) as orange oil and **82** (0.8 mg, 32%). IR (film), 3391, 2924, 1718 and 1623 cm⁻¹; δ_H (CDCl₃), 1.37 (3H, s), 1.54 (3H, s), 2.91 (1H, dd, $J=8.4, 13.6$ Hz), 3.08 (1H, dd, $J=8.4, 13.6$ Hz), 3.21 (3H, s), 3.82 (3H, s), 4.50 (3H, s), 4.76 (1H, t, $J=8.4$ Hz), 7.63 (1H, t, $J=8.0$ Hz), 7.83 (1H, d, $J=8.0$ Hz), 7.91 (1H, td, $J=8.0, 2.0$ Hz), 8.56 (1H, dd, $J=8.0, 2.0$ Hz), 16.21 (1H, s); δ_C (CDCl₃), 17.7, 25.8, 37.4, 39.6, 54.1, 59.9, 85.6, 109.4, 114.2, 116.4, 124.9, 126.3, 126.6, 132.5, 134.5, 137.7, 141.2, 155.1, 164.6, 178.1, 186.3; HRMS (FAB) calcd for C₂₁H₂₄NO₅ (M+H) 370.1654, found: m/z 370.1656

参考文献

- 1) a) Qu, J.; Liang, Q.; Luo, G.; Wang, Y. *Anal. Chem.* **2004**, *76*, 2239-2247. b) Fernandez-Ocaa, A. M.; Gomez-Rodriguez, M. V.; Velasco-Negueruela, A.; Camacho-Simarro, A. M.; Fernandez-Lpez, C.; Altarejos, J. *J. Agric. Food. Chem.* **2004**, *52*, 6414-6417. c) Katayama, S.; Mine, Y. *J. Agric. Food. Chem.* **2006**, *54*, 3271-3276. d) Tanaka, H.; Fukuda, N.; Shoyama, Y. *J. Agric. Food. Chem.* **2007**, *55*, 3783-3787. e) Recio, M. C.; Just, M. J.; Giner, R. M.; Manez, S.; Rios, J. L.; Hostettmann, K. *J. Nat. Prod.* **1995**, *58*, 140-144. f) Liu, Z.; Jia, Z.; Cates, R. G.; Li, D.; Owen, N. L. *J. Nat. Prod.* **1995**, *58*, 184-188. g) Nishimura, K.; Fukuda, T.; Miyase, T.; Noguchi, H.; Chen, X-M. *J. Nat. Prod.* **1999**, *62*, 1061-1064. h) Park, K. H.; Park, J.; Koh, D.; Lim, Y. *Phytother. Res.* **2002**, *16*, 359-363.
- 2) a) Firestone, R. A.; Pisano, J. M.; Falck, J. R.; McPhaul, M. M.; Krieger, M. *J. Med. Chem.* **1984**, *27*, 1037-1043. b) Counsell, R. E.; Kulkarni, P. G.; Afiatpour, P.; Ranade, V. V. *J. Med. Chem.* **1973**, *16*, 945-947.
- 3) a) Matsumoto, K.; Akazawa, K.; Murakami, Y.; Shimizu, M.; Ichiki, H.; Maruno, M.; Watanabe, H. *J. Trad. Med.* **1997**, *14*, 163-168. b) Hatakeyama, S.; Kawamura, M.; Yakano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081-4082.
- 4) a) Miyazawa, M.; Shimamura, H.; Nakamura, S.; Kameoka, H. *J. Agric. Food. Chem.* **1996**, *44*, 1647-1650. b) Kim, H-K.; Tak, J-H.; Ahn, Y-J. *J. Agric. Food. Chem.* **2004**, *52*, 7857-7861. c) Xu, H.; Zhang, N.; Casida, J. E. *J. Agric. Food. Chem.* **2003**, *51*, 2544-2577.
- 5) Isolation: Schmid, W. *Liebigs Ann. Chem.* **1855**, *93*, 83-88. Structure determination: Yates, P.; Stout, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 1691-1700.
- 6) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, *43*, 291-293.
- 7) Hamada, M.; Iikubo, K.; Ishikawa, Y.; Ikeda, A.; Umezawa, K.; Nishiyama, S. *Bioorg. Med. Chem. Lett.* **2003**, *19*, 3151-3153.
- 8) Okudaira, C.; Ikeda, Y.; Kondo, S.; Furuya, S.; Hirabayashi, Y.; Koyano, T.; Saito, Y.; Umezawa, K. *J. Enzym. Inhib.* **2000**, *15*, 129-138.
- 9) Oonishi, H.; Nagatsu, M.; Hasegawa, H.; Nozawa, S. Jpn. Kokai Tokkyo

Koho, 08217672, 27 Aug 1996, Heisei.

- 10) Zou, J.; Jin, D.; Chen, W.; Wang, J.; Liu, Q.; Zhu, X.; Zhao, W. *J. Nat. Prod.* **2005**, *68*, 1514-1518.
- 11) Wu, T-S.; Chen, C-M. *Chem. Pharm. Bull.* **2000**, *48*, 85-90.
- 12) Papageorgiou, M.; Fokialakis, N.; Mitaku, S.; Skaltsounis, A-L. *J. Nat. Prod.* **2000**, *63*, 385-386.
- 13) Balunas, M. J.; Su, B.; Brueggemeier, R. W.; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 1161-1166.
- 14) a) Yamakuni, T.; Aoki, K.; Nakatani, K.; Kondo, N. Oku, H.; Ishiguro, K.; Ohizumi, Y. *Neurosci. Lett.* **2006**, *364*, 206-210. b) Nakatani, K.; Yamakuni, T.; Kondo, N.; Arakawa, T.; Oosawa, K.; Shimura, S.; Inoue, H.; Ohizumi, Y. *Mol. Pharmacol.* **2004**, *66*, 667-674. c) Nakatani, K.; Nakahata, N.; Arakawa, T.; Yasuda, H.; Ohizumi, Y. *Biochem. Pharmacol.* **2002**, *63*, 73-79.
- 15) Nishihama, Y.; Amano, Y.; Ogamino, T.; Nishiyama, S. *Electrochemistry*, **2006**, *74*, 609-611.
- 16) Kobayashi, K.; Nishiyama, S.; Sato, K.; Shibata, T. Jpn. Kokai Tokkyo Koho, 07153773 21 Jun 2007, Heisei.
- 17) a) Kesado, T.; Hashizume, T.; Asahi, Y. *Antibicrob. Agents Chemother.* **1980**, *17*, 912-917. b) Kropp, H.; Sundelof, J. G.; Kahan, J. S.; Kahan, F. M.; Birnbaum, J. *Antibicrob. Agents Chemother.* **1980**, *17*, 993-1000. c) Horadam, V. W.; Smilack, J. D.; Montogomery, C. L.; Werringloer, J. *Antibicrob. Agents Chemother.* **1980**, *18* 557-561. d) Stapleton, P. D.; Shah, S.; Anderson, J. C.; Hara, Y.; Hamilton-Miller, J. M. T.; Taylor, P. W. *Int. J. Antimicrob. Agents*, **2004**, *23*, 462-467.
- 18) Amano, Y.; Nishiyama, S.; *Tetrahedron Lett.* **2006**, *47*, 6505-6507.
- 19) Nishihama, Y.; Ogamino, T.; Shi, W. L.; Cha, B-Y.; Yonezawa, T.; Teruya, T.; Nagai, K.; Suenaga, K.; Woo, J-T.; Nishiyama, S. *Heterocycles*, 2008, in press.
- 20) Fokialakis, N.; Magiatis, P.; Chinou, I.; Mitaku, S.; Tillequin, H. *Chem. Pharm. Bull.* **2002**, *50*, 413-414.
- 21) Couge, B.; Tillequin, F.; Koch, M.; Sevenet, T. *Plant. Med. Phytother.* **1980**, *14*, 208-212.
- 22) Mitaku, S.; Pusset, J.; *Plant. Med. Phytother.* **1988**, *22*, 83-87.
- 23) Tillequin, F.; Baudouin, G.; Koch, M.; Sevenet, T. *J. Nat. Prod.* **1980**, *43*, 498-502.

- 24) Mitaku, S.; Skaltsounis, A. L.; Tillequin, H.; Koch, M.; Pusset, J.; Chauviere, G. *J. Nat. Prod.* **1986**, *49*, 1091-1095.
- 25) Mitaku, S.; Skaltsounis, A. L.; Tillequin, F.; Koch, M.; Pusset, J. *Ann. Pharm. Fr.* **1989**, *47*, 149-156.
- 26) Funayama, S.; Cordell, G. A. *J. Nat. Prod.* **1984**, *47*, 285-291.
- 27) Reisch, J.; Adesina, S. K.; Bergenthal, D. *Pharmazie*, **1985**, *40*, 811-812.
- 28) Skaltsounis, A. L.; Seddrati, L.; Tillequin, F.; Koch, M.; Pusset, J.; Sevenet, T. *Nat. Prod. Lett.* **1995**, *5*, 281-287.
- 29) Muriithi, M. W.; Abraham, W-R.; Addae-Kyereme, J.; Scowen, I.; Croft, S. L.; Gitu, P. M.; Kendrick, H.; Njagi, E. N. M.; Wright, C. W. *J. Nat. Prod.* **2002**, *65*, 956-959.
- 30) Coppola, G. M.; Schuster, H. F. *J. Heterocyclic Chem.* **1989**, *26*, 957-964.
- 31) Frye, S. V.; Johnson, M. C.; Valvano, N. L. *J. Org. Chem.* **1991**, *56*, 3750-3752.
- 32) Friedman, D.; Ginsburg, D. *J. Org. Chem.* **1958**, *23*, 16-17.
- 33) Ebel, H.; Knor, S.; Steglich, W. *Tetrahedron*, **2003**, *59*, 123-129.
- 34) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.
- 35) Lin, A. J.; Pardini, R. S.; Lillis, B. J.; Sartorelli, A. C. *J. Med. Chem.* **1974**, *17*, 668-672.
- 36) a) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449. b) Pellon, R. F.; Estevez-Braun, A.; Docampo, M. L.; Martin, A.; Ravelo, A. G. *Synlett*, **2005**, *10*, 1606-1608.
- 37) a) Denny, W. A.; Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1987**, *30*, 658-663. b) Lee, H. H.; Wilson, W. R.; Ferry, D. M.; Zijl, P.; Pullen, S. M.; Denny, W. A. *J. Med. Chem.* **1996**, *39*, 2508-2517.
- 38) Bongui, J-B.; Elomri, A.; Cahard, D.; Tillequin, F.; Pfeiffer, B.; Pierre, A.; Seguin, E. *Chem. Pharm. Bull.* **2005**, *53*, 1540-1546.
- 39) Das, J. P.; Sinha, P.; Roy, S. *Org. Lett.* **2002**, *18*, 3055-3058.
- 40) Gomes, C. A.; Cruz, T. G.; Andrade, J. L.; Milhazes, N.; Borges, F.; Marques, M. P. M. *J. Med. Chem.* **2003**, *46*, 5395-5401.
- 41) Nozoe, S.; Takahashi, A.; Nunosawa, Y.; Endo, T. Jpn. Kokai Tokkyo Koho, 06016597, 25 Jan 1994, Heisei.
- 42) Nikolaou, K. C.; Sasmal, P. K.; Xu, H.; Namoto, K.; Ritzen, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4225-4229.
- 43) Alvarez, M.; Feliu, L.; Ajana, W.; Joule, J. A.; Fernandez-Puentes, J. L. *Eur.*

J. Org. Chem. **2000**, 849-855.

- 44) Sittisombut, C.; Boutefnouchet, S.; Van-Dufat, H. T.; Tian, W.; Michel, S.; Koch, M.; Tillequin, F.; Pfeiffer, B.; Pierre, A. *Chem. Pharm. Bull.* **2006**, *54*, 1113-1118.
- 45) Lindlar, H. *Helv. Chim. Acta.* **1952**, *35*, 446-450.
- 46) Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron*, **2005**, *61*, 1909-1918.
- 47) Nagamani, S. A.; Norikane, Y.; Tamaoki, N. *J. Org. Chem.* **2005**, *70*, 9304-9313.
- 48) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2006**, *71*, 2787-2796.
- 49) a) Shinozuka, T.; Yamamoto, Y.; Hasegawa, T.; Saito, K.; Naito, S. *Tetrahedron Lett.* **2008**, *49*, 1619-1622. b) Tisdale, E. J.; Slobodov, I.; Yheodorakis, E. A. *Org. Biomol. Chem.* **2003**, *1*, 4418-4422.

謝辞

本研究を行うにあたり、直接の御指導を賜りました慶應義塾大学理工学部 西山繁 教授に深く感謝いたします。

本研究を行うにあたり、有益な御助言を頂きました慶應義塾大学理工学部 梅澤一夫 教授、慶應義塾大学理工学部 小山内州一 教授、慶應義塾大学理工学部 末永聖武 准教授に深く感謝いたします。

研究全般にわたり、適切な御助言を頂きました慶應義塾大学理工学部 石川裕一 助教、慶應義塾大学理工学部 小畠りか 助教、慶應義塾大学理工学部 照屋俊明 助教に深く感謝いたします。

生物活性試験を行って頂きました北里大学薬学部 供田洋 教授、中部大学応用生物学部 禹済泰 教授に深く感謝いたします。

X 線結晶構造解析を行って頂きました慶應義塾大学文学部 大場茂 教授に深く感謝いたします。

卒業研究において御指導頂いた小神野孝尚 博士に深く感謝いたします。

公私に渡りお世話になりました濱田基子 氏に深く感謝いたします。

最後に共に研究生活をすごし、まわりから支えてくださいました土居史尚 博士、天野良治 博士、小原大雅 氏、田邊貴將 氏、小鷲聡美 氏、飯嶋大輔 氏、横山理 氏、宇野加奈子 氏、他西山研究室の皆様へ深く感謝いたします。

2009年2月