JOC The Journal of Organic Chemistry

Article

The Total Synthesis of Tetarimycin A, (±)-Naphthacemycin A and (±)-Fasamycin A. Structure-Activity Relationship Studies against Drug-Resistant Bacteria

Jing-Kai Huang, Tsai-Ling Yang Lauderdale, Chun-Cheng Lin, and Kak-Shan Shia

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00802 • Publication Date (Web): 22 May 2018

ACS Publications

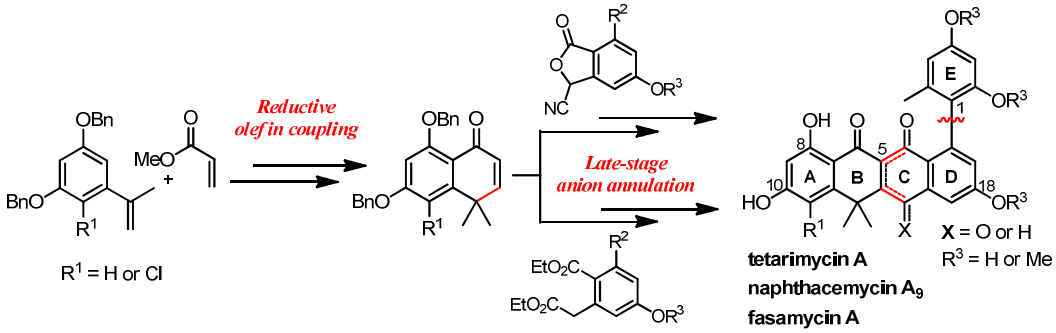
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

The Total Synthesis of Tetarimycin A, (±)-Naphthacemycin A_9 and (±)-Fasamycin A. Structure-Activity Relationship Studies against Drug-Resistant Bacteria

Jing-Kai Huang,[†,‡] Tsai-Ling Yang Lauderdale,[§] Chun-Cheng Lin,*[,†] and Kak-Shan Shia*[,‡]

[†]Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan, R.O.C.

[‡]Institute of Biotechnology and Pharmaceutical Research; [§]National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County 35053, Taiwan, R.O.C.



ABSTRACT: Making use of a reductive olefin coupling reaction and Michael-Dieckmann condensation as two key operations, we have completed a concise total synthesis of tetarimycin A, (±)-naphthacemycin A_9 and (±)-fasamycin A in a highly convergent and practical protocol. Synthetic procedures thus developed have also been applied to providing related analogues for structure-activity relationship studies, thereof coming to a conclusion that the free hydroxyl group at C-10 is essential for exerting inhibitory activities against a panel of Gram-positive bacteria, including drug-resistant strains VRE and MRSA.

INTRODUCTION

A rapid increase in multidrug-resistant bacteria and slow development of new antibiotics have posed a great threat to global public health.[1] What's even worse, infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has become one of the most serious problems in hospitals due to its high mortality rate.[2] Though a few antibiotics, including vancomycin, linezolid, tigecycline and daptomycin, are claimed to be clinically effective against MRSA infections, however, drug-resistant strains have been observed in recent years.[3] Thus, developing new antibiotics against

these multidrug-resistant bacteria is urgently demanded in the modern society. As illustrated in Figure 1, a class of natural products possessing a gem-dimethyl tetracyclic carbon skeleton has been reported to show potent anti-MRSA activities.[4] Among them, fasamycin A and B were found to inhibit the FabF enzyme associated with the biosynthesis of type II fatty acid (FASII) in bacteria.[5] Other congeners (e.g., naphthacemycin A_9) not only showed activities against various MRSA strains, but also could overcome β-lactam resistance in a regimen combining with imipenem.[4g] Above biological features make this family of natural products become a potential hit and/or lead for further structural modifications to pursue novel antibiotics for infectious diseases, especially those in unmet medical needs.

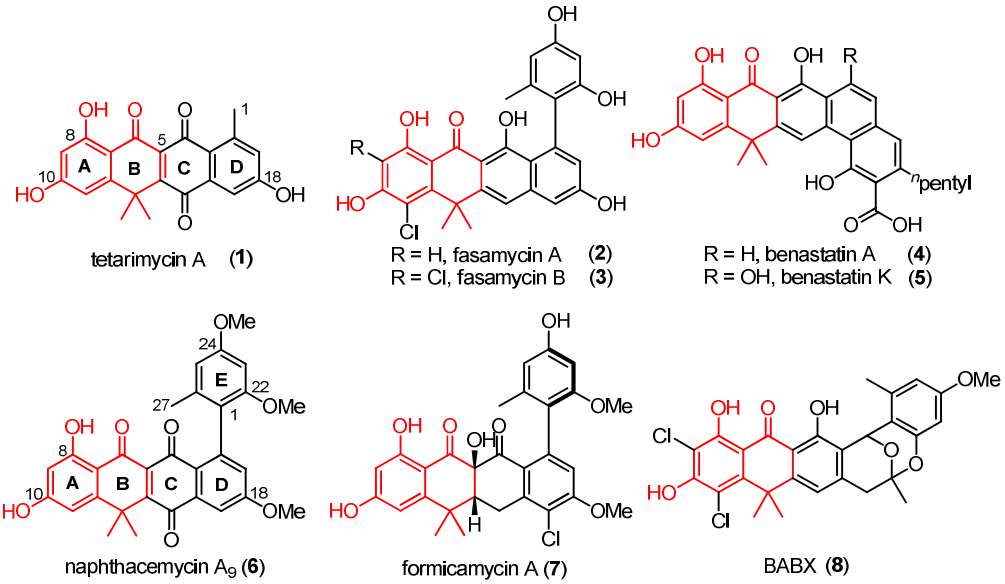


Figure 1. Structures of tetarimycin A and its congeners.

Recently, the total synthesis of tetarimycin A (**1**) and its congener (±)-naphthacemycin A_9 (**6**) have been achieved, respectively, by Shia and Sunazuka.[6] Although these synthetic sequences proved to be feasible, however, from the synthetic point of view, they remained lengthy, laborious and lacking of economic benefits.[7] Herein, we wish to report a general approach to construct linear gem-dimethyl tetracyclic skeletons, common in the titled natural products, in a more concise and practical manner. More importantly, both targeted products and related analogues could be rapidly synthesized to generate a library for structure-activity relationship (SAR) analysis against a panel of Gram-positive bacterial strains usually causing serious infections, including MSSA, MRSA and VRE. Results and discussion are presented as follows.

RESULTS AND DISCUSSION

Natural products **1** and **6** are structurally common in A, B, C and D rings with a major difference in E ring (methyl vs aryl). Target molecules **2** and **6** are structurally quite similar but possess a different oxidation state in C ring (phenol vs *p*-benzoquinone) as well as A ring (Cl vs H). Retrosynthetic analyses of these congeners are briefly illustrated in Figure 2.

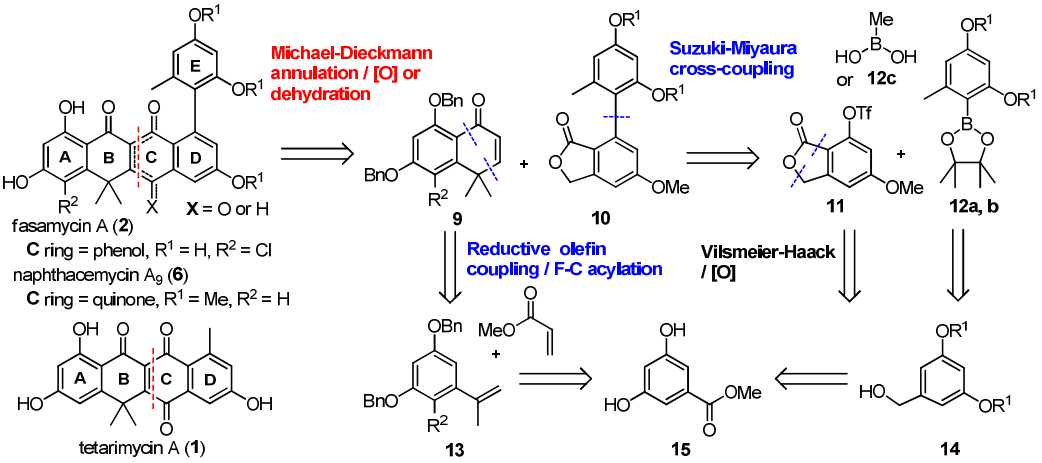
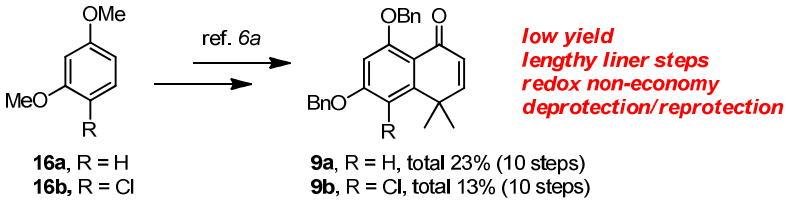


Figure 2. Retrosynthetic analyses of natural products **1**, **2** and **6**

It is envisioned that the linear tetracyclic nucleus might be constructed through the tandem Michael-Dieckmann condensation of fragments **9** and **10**.[8] Subsequently, the *p*-benzoquinone or phenol moiety in C ring should be achieved through either an oxidation or aromatization transformation. Lactone **10** could be readily prepared by a Suzuki-Miyaura coupling reaction of triflate **11** with boronic ester **12a-b** or methylboronic acid **12c**, which are commercially available or easily synthesized via documented procedures.[9] Enone **9** is proposed to be synthesized via a reductive olefin coupling between benzyl-protected **13** and methyl acrylate followed by intramolecular Friedel-Crafts acylation.[10] Indeed, based on our previous synthetic routes (Scheme 1; details outlined in Scheme S1), key fragment **9** was synthesized via a sequence of 10 steps in low yields (13~23%).[6a] Lengthy and laborious procedures made it difficult to achieve final products and related analogues in a sufficient amount for various bioactive tests and pharmacokinetic studies. Therefore, we decided to design a more concise sequence for enones **9a-b** starting from **13a-b**, which are commercially

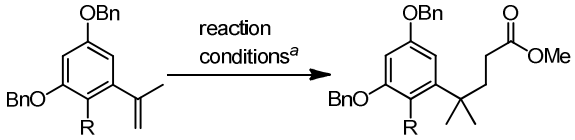
available or readily prepared according to synthetic procedures reported in the literature.[11]

Scheme 1. Preparation of Enones 9a-b via the Lengthy First-Generation Route



Since constructing the essential quaternary carbon center of intermediates **17a-b** was critical for the subsequent intramolecular Friedel-Crafts acylation, efforts on screening optimal coupling reaction conditions were intensively made. As listed in Table 1, an initial attempt to undergo free radical coupling using $Fe(acac)_3$ (30 mol%) and $PhSiH_3$ (3 equiv.) in one pot resulted in **17a** (entry 1) in low yield (38%).[10a] However, when $Fe(acac)_3$ was reduced to 10 mol% along with a slow addition of $PhSiH_3$ (3 equiv.) over 30 min (entry 4), the desired product could be obtained up to 58% yield. Further reducing the amount of $PhSiH_3$ from 3.0 to 1.5 equiv. and extending its addition time from 0.5 to 5 h via a syringe pump resulted in a high yield of **17a** (Table 1, entry 5, 91%). With compound **17a** in hand, the gem-dimethyl tetralone **18a** (Scheme 2) was readily prepared in 95% yield via a three-step sequence, involving the formation of carboxylic acid under basic hydrolysis followed by Friedel-Crafts acylation with TFAA and basic hydrolysis of the over-reactive product "enol trifloroacetate".[12]

Table 1. Screening optimal conditions for reductive olefin coupling

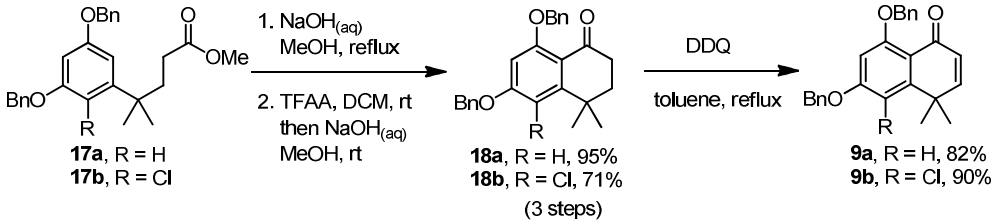


Entry	$Fe(acac)_3$	$PhSiH_3$	Solvent	yield of 17a	(17b)
1[b]	30 mol%	3.0 equiv.	EtOH/$(CH_2OH)_2$	38%	(-)
2[b]	10 mol%	3.0 equiv.	EtOH/$(CH_2OH)_2$	46%	(-)
3[b]	10 mol%	3.0 equiv.	DCE/$(CHOH)_2$	14%	(-)
4[c]	10 mol%	3.0 equiv.	EtOH/$(CH_2OH)_2$	58%	(-)
5[d]	10 mol%	1.5 equiv	EtOH/$(CH_2OH)_2$	91%	(68%)[e]

[a] All reactions were performed using styrene 1 (1 equiv.), methyl acrylate (3 equiv.), cat. $Fe(acac)_3$ and hydride source in solvent (0.2 M) at 60 °C under air. [b] One pot. [c] $PhSiH_3$ was slowly added over 30 min. [d] $PhSiH_3$ was slowly added over 5 h. [e] Solvent was degassed with Argon.

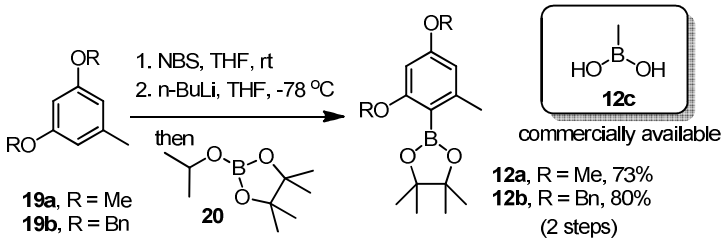
Oxidation of **18a** with DDQ in refluxing toluene afforded α,β-unsaturated tetralone **9a** in 82% yield.[13] Following a similar synthetic sequence (Scheme 2), enone **9b** was obtained in an overall yield of 63% starting from **17b**.

Scheme 2. Preparation for Benzyl-Protected Enone 9a-b



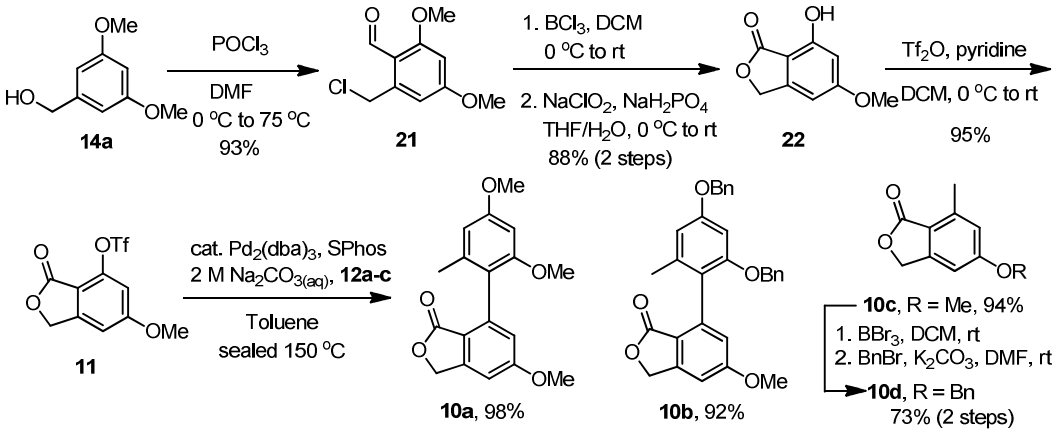
The newly designed 5-step sequence (71%) for tetralone **9a** is apparently much more concise than the 10-step one (23%) originally applied to the total synthesis of tetarimycin A.[6a] With this significant improvement in building the A-B ring, we then moved forward to construct the C-E fragments. According to Scheme 3, boronic esters **12a-b**, intended to establish the E ring existing in natural products **2** and **6**, were synthesized via a two-step sequence starting from **19a-b** in good yields (73~80%).

Scheme 3. Preparation of Boronic Esters 12a-b



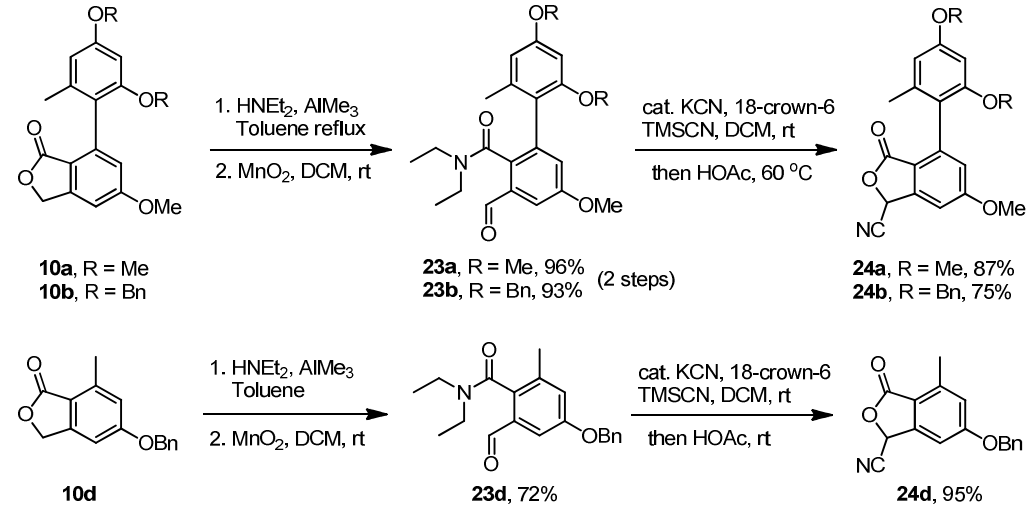
Lactones **10a-c**, serving as precursors for Hauser donors, could be prepared in a more general synthetic route according to Scheme 4. Benzyl alcohol **14a** could undergo Vilsmeier-Haack formylation in a regioselective manner with concomitant chlorination to give formyl benzylchloride **21** in high yield (93%).[14] Selective demethylation of **21** was achieved under treatment with boron trichloride to afford *o*-hydroxybenzaldehyde,[15] which was subjected to Pinnick oxidation followed by intramolecular lactonization to give lactone **22** in 88% over two steps. Under standard conditions, compound **22** was further converted to the corresponding triflate **11** in high yield (95%), which was then reacted with **12a-c** via Suzuki-Miyaura coupling to afford sterically crowded biphenyl lactones **10a-b** and methyl lactone **10c** in excellent yields (92~98%).[16]

Scheme 4. Synthesis of Lactones 10a-c via Suzuki-Miyaura Coupling



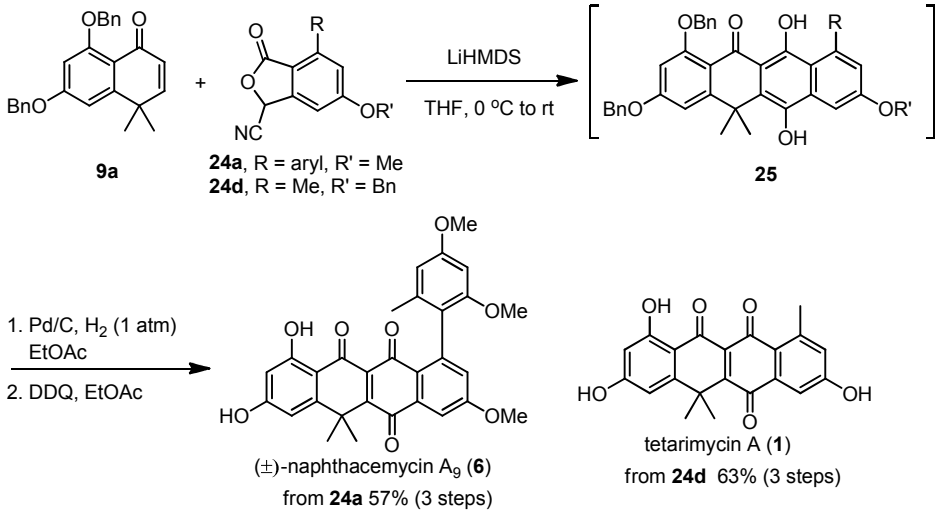
Based on **10c**, lactone **10d** was readily prepared via deprotection with BBr_3 followed by protection with BnBr in 73% over two steps. To approach natural products **1** and **6** as well as their related analogues to establish a library for the structure-activity relationship (SAR) analysis. Hauser donors **24a-b** and **24d** were then prepared according to Scheme 5. The lactone ring of compounds **10a-b** and **10d** was first opened up by treatment with diethylamine in the presence of $AlMe_3$ as catalyst to form the corresponding amide benzyl alcohols,[17] which without purification were oxidized by MnO_2 to give amide aldehyde **23a-b** and **23d**, respectively, in good to excellent yields (72~96%) over two steps. The aldehyde moiety thus formed was subjected to 1,2-addition with TMSCN followed by protonation with HOAc to give cyanohydrin by which intramolecular lactonization rapidly occurred to afford the corresponding cyanophthalides **24a-b** and **24d** in 75~95% yields.[18]

Scheme 5. Preparation of Hauser Donors 24a-b and **24d**



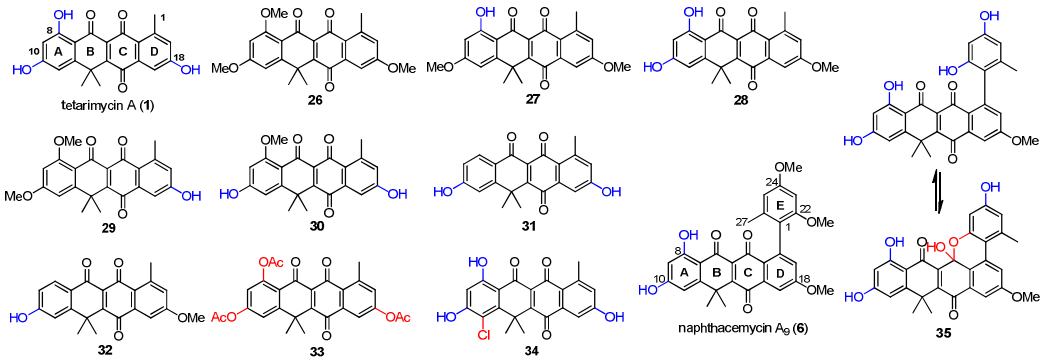
According to Scheme 6, the desired *p*-quinone motif in the C-ring could be efficiently constructed via Hauser-Kraus annulation to give the corresponding *p*-hydroquinone intermediate **25**, which without purification was subjected to hydrogenolysis under Pd/C followed by oxidation with DDQ to accomplish targets tetarimycin A (**1**) and (±)-naphthacemycin A_9 (**6**) in 57 and 63% yields, respectively, over three steps. Indeed, compound **25** was found to be partially oxidized to its *p*-quinone counterpart upon exposure to air in the crude residue.

Scheme 6. Completed Synthesis of Tetarimycin A and (±)-Naphthacemycin A_9



Similarly, following aforementioned synthetic strategies with minor peripheral modifications, structurally related analogues **26**~**35** were prepared for SAR studies against a panel of Gram-negative/positive bacterial strains as listed in Table 2.

Table 2. SAR of tetarimycin A (**1**) and (±)-naphthacemycin A_9 (**6**) against different bacterial strains.



Organism[a]	MIC[b] (μg/mL) of Compound

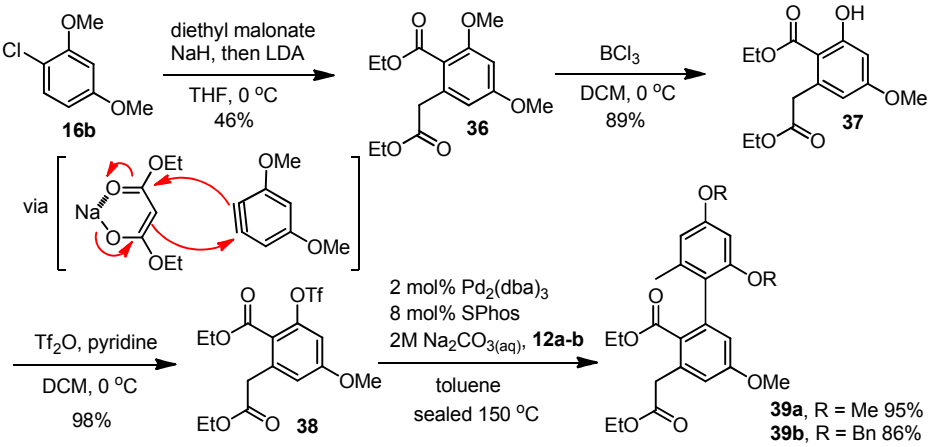
	1	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**6**	**35**	**V**[c]
Escherichia coli													
ATCC 25922	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Staphylococcus aureus													
ATCC 29213 (MSSA)	**1**	>8	>8	**1**	>8	>8	4	**2**	4	4	2	8	1
ATCC 43300 (MRSA)	**1**	>8	>8	**1**	>8	>8	4	**2**	8	4	2	8	1
M056 (MSSA)	**1**	>8	>8	**1**	>8	>8	4	**2**	8	4	2	4	1
N216 (MRSA)	**1**	>8	>8	**1**	>8	>8	4	**1**	4	2	2	4	1
Enterococcus faecalis													
ATCC 51299 (VRE)	**2**	>8	>8	**2**	>8	>8	4	**2**	8	**<0.5**	2	4	>8

[a] *E. coli*, Gram-negative bacteria; *S. aureus* and *E. faecalis*,Gram-positive bacteria; ATCC, American Type Culture Collection; M056 and N216, clinical isolates; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci. [b] MIC, minimum inhibitory concentration. [c] **V** = Vancomycin.

The current SAR study reveals that the hydroxyl group at C-10 is less tolerated than that on C-18. As demonstrated by natural product **1** and its analogue **28** (Table 2), both exhibited equally potent activity against MSSA, MRSA and VRE strains at a low MIC value (1 or 2 μg/mL) even if the free C-18 hydroxyl group was blocked. In sharp contrast, a complete loss of activity was observed once the C-10 hydroxyl group was blocked as exemplified by compounds **26**, **27** and **29**. In addition, keeping the molecule in a coplanar manner appeared important to show inhibitory activity against bacteria in that when the C-8 hydroxyl group was transformed to the methoxy, compound **30** (MIC > 8 μg/mL) resulted in a complete loss of activity against all strains tested. This inference is further supported by the fact that when the C-8 hydroxyl group of **30** is eliminated, inhibitory activities of resulting compounds **31** (MIC = 4 μg/mL) and **32** (MIC = 1 or 2 μg/mL) can be recovered by 2 to 4-fold. Compound **31** relative to **32** also suggests that the C-18 position is in favor of lipophilic interactions (e.g., Van der Waals attraction). To our surprise, compound **33**, as fully blocked with the acetyl group, exhibited a moderate activity (MIC = 4 μg/mL) against ATCC 29213 and N216 strains. These unexpected outcomes may be ascribed to the partial hydrolysis of the acetate functionality at C-10 during assays. More importantly, as compared to natural **1**, compound **34** (MIC < 0.5 μg/mL) with an additional chlorine atom at C-11 displayed a dramatic improvement in activity against a VRE strain (ATCC 51299), indicating that structural modifications of this position might lead to the identification of a potential agent against VRE strains. Natural product **6** with slightly weaker bioactivities than **28** implied that a bulky hydrophobic

group might not be necessary for C-1 position. All tested compounds in Table 2 possess a MIC > 8 μg/mL against a Gram-negative strain (ATCC 25922) and thus, we tentatively assume that natural products **1** and **6**, and their structurally related analogues could be Gram-positive-specific inhibitors. Mechanistically, tetarimycin A (**1**) and (±)-naphthacemycin A_9 (**6**) are supposed to inhibit an enzyme called FabF in that it has been identified as a molecular target of their congeners fasamycins A and B by Brady.[5] Since fasamycin A (**2**) possesses a phenol unit rather than *p*-benzoquinone in the C ring, instead of cyanophthalides for performing Hauser-Kraus annulation, homophthalate compounds **39a-b** were then elaborated to carry out traditional Michael-Dieckmann condensation (Scheme 7).[19] Commercially available **16b** and diethyl malonate dissolved in THF were first treated with NaH to deprotonate diethyl malonate followed by addition of a second base LDA to form benzyne *in situ*. Malonate enolate was then reacted with benzyne to afford diester **36** in 46% yield along with an inevitable side product formed via addition of diisopropylamine to benzyne.[20] Selective demethylation could take place under treatment with BCl_3 to give phenol **37** (89%), which was converted to triflate **38** in 98% yield under standard conditions followed by coupling with **12a-b** to yield compounds **39a-b** in 95% and 86%, respectively.

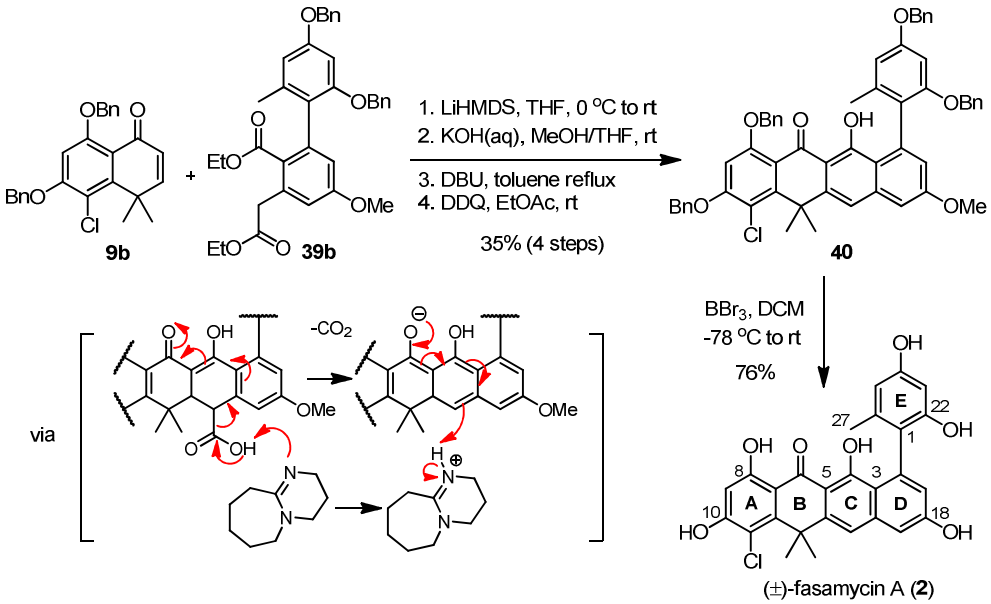
Scheme 7. Preparation of 39a-b for Michael-Dieckmann Condensation



With Michael donor **39b** and acceptor **9b** in hand, a 4-step synthetic sequence (Scheme 8), involving Michael-Dieckmann condensation with lithium base, basic hydrolysis with $KOH_{(aq)}$, decarboxylation with DBU and aromatization with DDQ, was carried out to give intermediate **40** in an overall yield of 35%.[19c] Finally, full deprotection of compound **40** could be fulfilled under treatment with BBr_3 to achieve the first total synthesis of (±)-fasamycin A (**2**) in 76% yield, which was first isolated

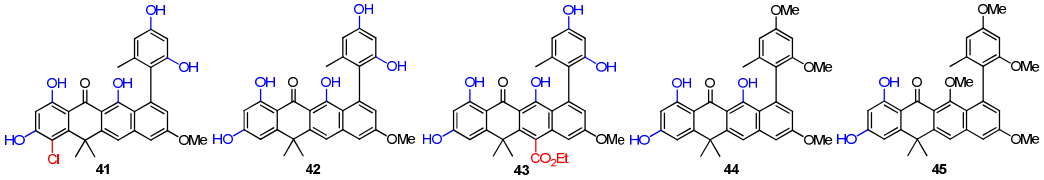
and reported by Brady in 2011.[4d] In a similar synthetic manner, analogues **41-45** listed in Table 3 were also synthesized for SAR analysis.

Scheme 8. Completed Synthesis of (±)-Fasamycin A



In general, compounds with a phenol C ring (Table 3) are inferior to those with a *p*-benzoquinone unit (Table 2) in showing activities against bacterial strains examined. As natural product **2** was compared to analogue **34** (Table 2), it clearly indicated that replacing the methyl group with a crowded 1,3-diphenol unit at C-1 position was totally unfavorable, resulting in an almost loss of activities (MIC $\geq$ 8 μg/mL) against all strains tested, with the exception that a moderate activity (MIC = 2 μg/mL) against VRE (ATCC 51299) was observed, presumably due to the halogen effect (Cl) at C-11 position. Analogues **41-43** (MIC = 2~4 μg/mL) in comparison with parental **2** (MIC = 2~8 μg/mL) again supported that a hydrophobic group (e.g., a methoxy moiety) at C-18 could enhance anti-bacterial potency. When the free hydroxyl group of the E ring was fully blocked, compounds **44** and **45** (MIC = 8 μg/mL) thus obtained with a dramatic drop in activities suggested that a bulky hydrophobic group at C-1 was inappropriate.

Table 3. SAR of (±)-fasamycin A (**2**) against different bacterial strains.



Organism[a]	MIC[b] (μg/mL) of Compound						
	2	**41**	**42**	**43**	**44**	**45**	**V**[c]
Escherichia coli							
ATCC 25922	>8	>8	>8	>8	>8	>8	>8
Staphylococcus aureus							
ATCC 29213 (MSSA)	>8	4	4	4	>8	>8	1
ATCC 43300 (MRSA)	8	4	4	4	8	>8	1
M056 (MSSA)	8	4	2,4	2,4	>8	>8	1
N216 (MRSA)	8	4	2	2	>8	>8	1
Enterococcus faecalis							
ATCC 51299 (VRE)	2	4	4	4	4	>8	>8

[a] *E. coli*, Gram-negative bacteria; *S. aureus* and *E. faecalis*,Gram-positive bacteria; ATCC, American Type Culture Collection; M056 and N216, clinical isolates; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant enterococci. [b] MIC, minimum inhibitory concentration. [c] **V** = Vancomycin.

CONCLUSION

We have completed a concise total synthesis of tetarimycin A, (±)-naphthacemycin A_9 and (±)-fasamycin A in a highly convergent and practical protocol, mainly making use of a reductive olefin coupling in the early stage and Michael-Dieckmann condensation in the late stage as two key operations. Based on the current SAR studies, several important conclusions could be derived as follows: 1) the free hydroxyl group at C-10 is structurally required for displaying anti-bacterial activities; 2) a *p*-benzoquinone unit in the C ring is superior to the corresponding phenol unit; 3) the free hydroxyl group at C-18 is structurally modifiable and preferable to the lipophilic functionality; 4) the Cl atom at C-11 has a particularly beneficial effect against the VRE strain; 5) the E-ring shows preference to having a smaller hydrophobic group rather than a bulky one.

EXPERIMENTAL SECTION

Chemistry General. All reactions were performed under nitrogen unless otherwise stated. All solvents and reagents were employed as received without further purification. Analytical thin layer chromatography was performed on SiO_2 60 F-254 plates and flash column chromatography was carried out using SiO_2 60 (particle size 0.040-0.055 mm, 230–400 mesh). Visualization was performed under UV irradiation at 254 nm followed by staining with aqueous potassium permanganate and charring by heat gun. Infrared spectra (IR) were recorded on a FT-IR spectrometer and expressed in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. Chloroform-d was used as the solvent and TMS (δ = 0.00 ppm) as an internal standard (δ = 77.00 for ^{13}C-NMR). Acetone-d_6 was used as the solvent (δ = 2.05 for ^1H-NMR, δ = 29.29 for ^{13}C-NMR). DMSO-d_6 was used as the solvent (δ = 2.50 for ^1H-NMR, δ = 39.51 for ^{13}C-NMR). Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), qd (quartet of doubles), tt (triplet of triplets), ddd (doublet of doublet of doublets), m (multiplet), br (broad). Coupling constants (*J*) are expressed in Hz. HRMS was obtained on a triple quadrupole mass analysis using electrospray ionization (ESI) source or a double quadrupole mass analysis using electron impact (EI) source, and spectral data were recorded as m/z values. Melting points were measured using an Electrothermal instrument.

Methyl 4-(3,5-bis(benzyloxy)phenyl)-4-methylpentanoate (17a). To a stirred solution of styrene **13a** (1.7 g, 5.0 mmol) methyl acrylate (1.3 g, 15.0 mmol) and cat. $Fe(acac)_3$ (176 mg, 0.50 mmol) in EtOH/ethylene glycol (20 mL/5 mL), which was degassed with argon, was added phenylsilane (812 mg, 7.50 mmol) over 5 h via syringe pump at 60 □. After reaction was complete, the solvent was evaporated to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:20) followed by EtOAc/*n*-hexane (1:10) to afford ester **17a** (1.9 g, 91%) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2952, 2871, 1736, 1593, 1454, 1434, 1158; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27 (s, 6H), 1.92 (dd, *J* = 10.8, 6.8 Hz, 2H), 2.04 (dd, *J* = 10.8, 6.8 Hz, 2H), 3.61 (s, 3H), 5.02 (s, 4H), 6.47 (t, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 2H), 7.31-7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.6, 29.9, 37.5, 38.8, 51.4, 70.0, 98.8, 105.8, 127.6, 127.9, 128.5, 136.9, 150.6, 159.8, 174.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{30}O_4Na$ 441.2036, found: 441.2038.

Methyl 4-(3,5-bis(benzyloxy)-2-chlorophenyl)-4-methylpentanoate (17b). According to the synthetic procedures similar to compound **17a**, ester **17b** (12.3 g, 68% yield) was prepared from styrene **13b** (14.6 g, 40.0 mmol) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2951, 2927, 2874, 1736, 1592, 1579, 1434,

1169; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.45 (s, 6H), 2.01 (dd, J = 11.6, 8.4 Hz, 2H), 2.35 (dd, J = 11.6, 8.4 Hz, 2H), 3.61 (s, 3H), 5.00 (s, 2H), 5.08 (s, 2H), 6.55 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H), 7.33-7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 30.2, 34.6, 39.5, 51.4, 70.2, 71.0, 99.7, 108.1, 115.0, 127.0, 127.5, 127.8, 128.1, 128.5, 128.6, 136.4, 136.4, 145.7, 155.5, 157.2, 174.2; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{27}H_{30}ClO_4$ 453.1827, found: 453.1836.

6,8-Bis(benzyloxy)-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (18a). To a stirred solution of ester **17a** (12.6 g, 30.0 mmol) in MeOH (60 mL) was added $NaOH_{(aq)}$ (4 N, 10 mL, 40.0 mmol) at room temperature under N_2. The resulting mixture was then stirred at reflux temperature under N_2 for 3 h. After reaction was complete, the solvent was evaporated to give the crude residue, which was neutralized with 5% $HCl_{(aq)}$ to pH~4. EtOAc (60 mL x 2) was then added to extract water layer. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the corresponding acid (12.1 g, quantity). To a stirred solution of acid in dry DCM (120 mL), which was degassed with argon, was added TFAA (9.5 g, 45.0 mmol) at 0 □ under N_2. The resulting mixture was then stirred at room temperature under N_2 for 3 h. After reaction was complete, the $NaOH_{(aq)}$ (4 N, 12 mL, 48.0 mmol) in MeOH (60 mL) was added to quench and hydrolyze the overreacted product enol trifloroacetate at 0 □. The solvent of resutling mixture was evaporated, and extracted with EtOAc (60 mL x 2). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized with diethyl ether and *n*-hexane to afford tetralone **18a** (11.0 g, 95% yield over 2 steps) as a white solid: mp = 114–115 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3032, 2961, 2926, 2864, 1670, 1595, 1568, 1324, 1157; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 6H), 1.93 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 5.08 (s, 2H), 5.14 (s, 2H), 6.48 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 2.2 Hz, 1H), 7.29-7.43 (m, 8H), 7.58 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.7, 34.8, 36.4, 36.6, 70.0, 70.5, 98.7, 104.1, 115.9, 126.6, 127.5, 127.6, 128.2, 128.4, 128.6, 136.0, 136.6, 156.7, 161.0, 163.0, 196.0; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{26}H_{27}O_3$ 387.1955, found: 387.1956.

6,8-Bis(benzyloxy)-5-chloro-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (18b). According to the synthetic procedures similar to compound **18a**, tetralone **18b** (18.8 g, 71% yield over 2 steps) was prepared from ester **17b** (12.0 g, 26.5 mmol) as a white solid: mp = 105–106 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3031, 2959, 2932, 2868, 1682, 1576, 1309, 1226; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.63 (s, 6H), 1.99 (t, J = 6.4 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 5.09 (s, 2H), 5.11 (s, 2H), 6.53 (s, 1H), 7.30-7.52 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.7, 36.8, 36.9, 40.4, 70.8, 71.3, 99.0, 115.1,

118.1, 126.8, 127.0, 127.8, 128.2, 128.6, 128.7, 135.7, 136.4, 150.8, 158.5, 159.1, 196.4; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{26}H_{26}ClO_3$ 421.1565, found: 421.1577.

6,8-Bis(benzyloxy)-4,4-dimethylnaphthalen-1(4H)-one (9a). To a stirred solution of tetralone **18a** (3.9 g, 10.0 mmol) in dry toluene (50 mL) was added DDQ (2.4 g, 10.5 mmol) in one portion. The resulting mixture was then stirred at reflux temperature under N_2 for 2 h. After reaction was complete, the reaction mixture was filtrated with celite, and quenched with saturated $NaHCO_{3(aq)}$ (20 mL) and extracted with EtOAc (50 mL). The organic extract was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with DCM/*n*-hexane (1:1) followed by DCM/EtOAc (10:1) and further recrystallized with diethyl ether and *n*-hexane to afford enone **9a** (3.2 g, 82% yield) as a white solid: mp = 139–140 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2966, 2929, 2875, 1659, 1633, 1597, 1455, 1322, 1169; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 6H), 5.09 (s, 2H), 5.18 (s, 2H), 6.24 (d, J = 10.0 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.66 (d, J = 10.0 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 7.25-7.63 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.4, 37.8, 70.0, 70.5, 99.2, 104.7, 114.9, 126.5, 127.4, 127.5, 128.1, 128.2, 128.4, 128.6, 135.9, 136.6, 152.8, 154.6, 161.1, 162.2, 183.7; HRMS (EI) m/z: [M] calcd. for $C_{26}H_{24}O_3$ 384.1725, found: 384.1729.

6,8-Bis(benzyloxy)-5-chloro-4,4-dimethylnaphthalen-1(4H)-one (9b). According to the synthetic procedures similar to compound **9a**, enone **9b** (3.8 g, 90% yield) was prepared from tetralone **18b** (4.2 g, 10.0 mmol) as a white solid: mp = 117–118 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2959, 2935, 2867, 1587, 1430, 1314, 1209; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.73 (s, 6H), 5.14 (s, 4H), 6.18 (d, J = 10.4 Hz, 1H), 6.60 (d, J = 10.4 Hz, 1H), 6.63 (s, 1H), 7.31-7.45 (m, 8H), 7.55 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0, 39.1, 70.9, 71.3, 99.6, 114.7, 116.7, 125.3, 126.8, 127.0, 127.7), 128.2, 128.5, 128.7), 135.6, 136.4, 148.9, 155.8, 158.0, 159.6, 184.1; HRMS (ESI) m/z: [M + Na]$^+$ calcd. for $C_{26}H_{23}ClO_3Na$ 441.1228, found: 441.1228.

2-(2,4-Dimethoxy-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12a). To a stirred solution of compound **19a** (4.1 g, 26.6 mmol) in THF (133 mL) was added NBS (5.0 g, 27.9 mmol) portionwise at room temperature. The resulting mixture was then stirred at room temperature under N_2 for 15 h. After reaction was complete, the reaction mixture was quenched with 5% $Na_2S_2O_{3(aq)}$ (30 mL) and extracted with EtOAc (50 mL). The organic extract was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford the corresponding bromobenzene. To a stirred solution of the intermediate bromobenzene (5.9 g, 25.5 mmol) in dry THF (51 mL) at -78 □ was added n-BuLi (2.5 M in *n*-hexane, 10.2 mL, 25.5 mmol) dropwise under N_2. After the reaction mixture was

stirred at -78 □ under N_2 for 30 mins, the boric ester **20** (5.0 g, 26.8 mmol) was added in one portion. Then the reaction mixture was allowed to react at room temperature under N_2 for 30 min. After reaction was complete, the reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) at 0 □ and extracted with EtOAc (50 mL). The organic extract was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford boronic ester **12a** (5.4 g, 73% yield over 2 steps) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2977, 2937, 2838, 1604, 1579, 1455, 1515, 1201, 1146; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 12H), 2.34 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 6.22 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0, 24.6, 54.9, 55.3, 83.2, 94.9, 106.3, 144.2, 161.7, 164.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{15}H_{23}BO_4Na$ 301.1582, found: 301.1581.

2-(2,4-Bis(benzyloxy)-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12b). According to the synthetic procedures similar to compound **12a**, boronic ester **12b** (10.3 g, 80% yield over 2 steps) was prepared from compound **19b** (9.1 g, 30.0 mmol) as a white solid: mp = 113–114 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2977, 2929, 2867, 1601, 1575, 1372, 1338, 1159, 1144; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (s, 12H), 2.35 (s, 3H), 4.98 (s, 2H), 5.03 (s, 2H), 6.37 (d, J = 1.6 Hz, 1H), 6.40 (d, J = 1.6 Hz, 1H), 7.28-7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.2, 24.8, 69.8, 70.1, 77.2, 83.4, 97.1, 107.9, 127.5, 127.6, 127.9, 128.2, 128.5, 137.0, 137.3, 144.7, 161.0, 163.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{31}BO_4Na$ 453.2208, found: 453.2207.

2-(Chloromethyl)-4,6-dimethoxybenzaldehyde (21). To a stirred dry DMF (12 mL) at 0 □ was added $POCl_3$ (5.6 mL, 60 mmol) dropwise under N_2. After the reaction mixture was stirred at room temperature for 30 mins, benzyl alchol **14a** (7.1 g, 42.2 mmol) was added at 0 □. Then the reaction mixture was allowed to react at 75 □ under N_2 for 2 h. The reaction mixture was added portionwise to stirred ice water (50 mL) to quench the reaction. $NaOH_{(aq)}$ was then added to neturalize the reaction mixture to pH~7. EtOAc (60 mL x 2) was then added to extract water layer. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized with EtOAc and *n*-hexane to afford benzaldehyde **21** (8.5 g, 93% yield) as a white solid:[14] mp = 70–71 □; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.90 (s, 6H), 5.05 (s, 2H), 6.44 (s, 1H), 6.76 (s, 1H), 10.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.8, 55.6, 56.0, 97.6, 107.5, 115.9, 142.3, 165.0, 165.3, 189.9.

7-Hydroxy-5-methoxyisobenzofuran-1(3H)-one (22). To a stirred solution of **21** (9.7 g, 45.2 mmol) in dry DCM (180 mL) at 0 □ was added BCl_3 (1M in DCM, 60 mL, 60 mmol) under N_2. After stirred at room temperature for 7 h, the reaction was

quenched with ice water at 0 □. The organic layer was washed with sat. $NaHCO_{3(aq)}$ and water, dried over $MgSO_4$, filtered and concentrated to give the crude phenol, which without purification was oxidized by pinnick reaction. To a stirred solution of the intermediate phenol (8.8 g, 43.9 mmol) NaH_2PO_4 (15.6 g, 130 mmol) and 2-methyl-2-butene (13 mL) in THF/*t*BuOH/H_2O (80 mL/80 mL/40 mL) was added $NaClO_2$ (11.8 g, 130.6 mmol) portionwise at 0 □. After stirred at room temperature for 3 h, THF (80 mL x 2) was added to extract the reaction mixture. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized with THF and *n*-hexane to afford compound **22** (7.1 g, 88% yield over 2 steps) as a white solid:[21] mp = 183–185 □; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 3.79 (s, 3H), 5.17 (s, 2H), 6.39 (d, J = 2.0 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 55.8, 68.4, 98.4, 101.4, 104.4, 151.6, 157.9, 165.8, 168.4.

6-Methoxy-3-oxo-1,3-dihydroisobenzofuran-4-yl trifluoromethanesulfonate (11). To a stirred solution of phenol **22** (7.0 g, 38.9 mmol) and pyridine (20 mL) in dry DCM (40 mL) at 0 □ was slowly added trifluoromethanesulfonic anhydride (12.1 g, 42.9 mmol) under N_2. After stired at room temperature for 2 h, reaction was quenched with ice water. The aqueous layer was separated and extracted with DCM (50 mL x 2). The organic portions were combined, washed with 5% $HCl_{(aq)}$, and water, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized with EtOAc and *n*-hexane to afford compound **11** (11.5 g, 95% yield) as a white solid: mp = 141–142 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3112, 3055, 2986, 2951, 2850, 1757, 1625, 1426, 1226, 1197; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94 (s, 3H), 5.28 (s, 2H), 6.90 (s, 1H), 6.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.6, 68.8, 106.1, 110.1, 110.8, 118.7 (q, $J_{F\text{-}C}$ = 319 Hz), 146.7, 151.1, 166.0, 166.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{10}H_7F_3O_6SNa$ 334.9808, found: 334.9808.

Ethyl 2-(2-Ethoxy-2-oxoethyl)-4-methoxy-6-(((trifluoromethyl)sulfonyl)oxy)benzoate (38). According to the synthetic procedures similar to compound **11**, triflate **38** (6.1 g, 98% yield) was prepared from phenol **37** (4.2 g, 14.9 mmol) as a white solid:[22] mp = 60–62 □; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, J = 7.2 Hz, 3H), 1.38 (t, J = 7.2 Hz, 3H), 3.85 (s, 3H), 3.89 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 2.6 Hz, 1H), 6.83 (d, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 14.1, 40.1, 55.9, 61.2, 62.0, 107.1, 117.0, 118.6 (q, $J_{F\text{-}C}$ = 319 Hz), 119.0, 138.1, 148.8 , 161.5, 164.4, 170.2.

7-(2,4-Dimethoxy-6-methylphenyl)-5-methoxyisobenzofuran-1(3H)-one (10a). To a stirred solution of triflate **11** (3.36 g, 10.8 mmol) and boronic ester **12a** (6.0 g, 21.6 mmol) in toluene(60 mL) was added cat. $Pd_2(dba)_3$ (198 mg, 0.20 mmol), Sphos (369

mg, 0.90 mmol) and 2M $Na_2CO_{3(aq)}$ (22 mL). After degass with argon for 30 mins, the reaction vial was sealed and then allowed to react at 150 □ under N_2 for 2 h. The reaction mixture was diluted with EtOAc (40 mL) and filtrated with celite. The layers were separated, and the aqueous layer was extracted with EtOAc (50 mL). The organic portions were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford biphenyl lactone **10a** (3.3 g, 98% yiled) as a white solid: mp = 147–148 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3059, 3001, 2939, 2841, 1756, 1608, 1594, 1478, 1465, 1337, 1213, 1201, 1154; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.05 (s, 3H), 3.67 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 5.22 (s, 2H), 6.41 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.82 (d, J = 3.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2, 54.9, 55.4, 55.5, 67.9, 95.8, 104.6, 106.2, 116.3, 117.9, 118.8, 137.5, 139.1, 149.7, 157.6, 160.0, 163.9, 169.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{18}H_{18}O_5Na$ 337.1046, found: 337.1048.

7-(2,4-Bis(benzyloxy)-6-methylphenyl)-5-methoxyisobenzofuran-1(3H)-one (10b). According to the synthetic procedures similar to compound **10a**, biphenyl lactone **10b** (2.2 g, 92% yield) was prepared from triflate **11** (1.6 g, 5.1 mmol) and boronic ester **12b** (4.3 g, 10.0 mmol) as a white solid: mp = 139–140 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3063, 3031, 2937, 2875, 1755, 1607, 1477, 1454, 1337, 1213, 1153; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.08 (s, 3H), 3.88 (s, 3H), 4.94 (d, J = 13.0 Hz, 1H), 4.97 (d, J = 13.0 Hz, 1H), 5.04 (s, 2H), 5.16 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 15.2 Hz, 1H), 6.53 (d, J = 2.2 Hz, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 7.12-7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 55.7, 68.0, 70.0, 70.3, 98.4, 104.9, 107.8, 116.8, 118.7, 119.0, 126.8, 127.4, 127.7, 128.0, 128.2, 128.6, 136.9, 137.2, 137.9, 139.5, 149.6, 157.0, 159.4, 164.0, 169.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{30}H_{26}O_5Na$ 489.1672, found: 489.1675.

5-Methoxy-7-methylisobenzofuran-1(3H)-one (10c). According to the synthetic procedures similar to compound **10a**, methylated lactone **10c** (838 mg, 94% yield) was prepared from triflate **11** (1.6 g, 5.1 mmol) and boronic acid **12c** (599 mg, 10.00 mmol) as a white solid: mp = 172–173 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3017, 2980, 2950, 2842, 1741, 1616, 1604, 1308, 1146; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.64 (s, 3H), 3.88 (s, 3H), 5.18 (s, 2H), 6.73 (s, 1H), 6.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.4, 55.6, 68.4, 103.5, 115.7, 117.3, 141.2, 149.8, 164.2, 170.9; HRMS (EI) m/z: [M] calcd. For $C_{10}H_{10}O_3$: 178.0630, found: 178.0632.

Ethyl 3-(2-Ethoxy-2-oxoethyl)-2',4',5-trimethoxy-6'-methyl-[1,1'-biphenyl]-2-carboxylate (39a). According to the synthetic procedures similar to compound **10a**, biphenyl diethyl homophthalate **39a** (794 mg, 95% yield) was prepared from triflate **38** (829 mg, 2.00 mmol) and boronic ester **12a** (1.4 g, 5.0 mmol) as a white solid: mp

= 84–85 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2979, 2938, 2839, 1735, 1713, 1602, 1498, 1465, 1318, 1277, 1201, 1155; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 2.02 (s, 3H), 3.66 (s, 3H), 3.72 (d, J = 16.4 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.92 (q, J = 7.2 Hz, 2H), 3.93 (d, J = 16.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 6.34 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 14.0, 20.4, 40.0, 55.1, 55.6, 60.1, 60.6, 95.7, 105.8, 115.2, 115.4, 122.9, 126.5, 134.9, 138.1, 139.3, 157.5, 159.5, 160.0, 168.2, 171.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{23}H_{28}O_7Na$ 439.1727, found: 439.1725.

Ethyl 2',4'-Bis(benzyloxy)-3-(2-ethoxy-2-oxoethyl)-5-methoxy-6'-methyl-[1,1'-biphenyl]-2-carboxylate (39b). According to the synthetic procedures similar to compound **10a** with reaction carried out for 15 h instead, biphenyl diethyl homophthalate **39b** (2.0 g, 86% yield) was prepared from triflate **38** (829 mg, 2.00 mmol) and boronic ester **12b** (2.6 g, 6.1 mmol) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2979, 2930, 2870, 1733, 1716, 1602, 1498, 1464, 1316, 1275, 1201, 1154; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.82 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 2.04 (s, 3H), 3.78 (d, J = 16.4 Hz, 1H), 3.80 (s, 3H), 3.91 (qd, J = 7.2, 1.6 Hz, 2H), 3.92 (d, J = 16.4 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.93 (s, 2H), 5.03 (s, 2H), 6.44 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.80 (d, J = 2.6 Hz, 1H), 7.16-7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.5, 14.1, 20.4, 40.1, 55.2), 60.2, 60.7, 70.0, 70.1, 98.3, 107.6, 115.1, 115.7, 123.9, 126.5, 126.5, 127.3, 127.5, 127.9, 128.2, 128.5, 135.0, 137.0, 137.3, 138.3, 139.6, 156.5, 158.6, 160.1, 168.3, 171.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{35}H_{36}O_7Na$ 591.2353, found: 591.2351.

5-(Benzyloxy)-7-methylisobenzofuran-1(3H)-one (10d). To a stirred solution of methyl-protecting lactone **10c** (2.8 g, 15.7 mmol) in dry DCM (15 mL) was added BBr_3 (4.0 g, 1.52 mL, 16.0 mmol) at 0 □ under N_2. The mixture was then allowed to react at room temperature under N_2 for 6 h. After reaction was complete, ice water (10 mL) was added to quench the reaction. DCM was then evaporated to give the crude residue,which was dissolved in THF/EtOAc (30 mL/20 mL) and filtrated with celite to remove bronic acid. The organic layer was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. To a stirred solution of the crude residue in DMF (10 mL) was added K_2CO_3 (2.2 g, 16.0 mmol) and benzyl bromide (2.7 g, 15.8 mmol) dropwise. The mixture was then allowed to react at room temperature under N_2 for 2 h. After reaction was complete, water (20 mL) was added to quench the reaction. The aqueous layer was separated and extrated with DCM (45 mL). The organic extract was washed with water (15 mL x 3) and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue,

which was recrystallized with diethyl ether and *n*-hexane to afford benzyl-protecting lactone **10d** (2.9 g, 73% yield over 2 steps) as a white solid: mp = 144–145 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3062, 3032, 2946, 2874, 1754, 1599, 1448, 1340, 1155, 1033; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.64 (s, 3H), 5.13 (s, 2H), 5.17 (s, 2H), 6.79 (s, 1H), 6.88 (s, 1H), 7.36-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.4, 68.4, 70.3, 104.4, 116.0, 118.1, 127.3, 128.2, 128.7, 135.8, 141.3, 149.8, 163.3, 170.8; HRMS (EI) m/z: [M] calcd. for $C_{16}H_{14}O_3$ 254.0943, found: 254.0950.

***N*,*N*-Diethyl-3-formyl-2',4',5-trimethoxy-6'-methyl-[1,1'-biphenyl]-2-carboxamide (23a).** To a stirred solution of diethyl amine (1.5 g, 20.5 mmol) in dry toluene (20 mL) was added $AlMe_3$ (2M in toluene, 10 mL, 20 mmol) dropwise at 0 □ under N_2. After stirred at room temperature for 30 min, lactone **10a** (3.1 g, 9.9 mmol) was added in one portion. The reaction mixture was then heated to reflux under N_2 for 15 h. After cooling, 5% $HCl_{(aq)}$ (20 mL) was slowly added at 0 □ to quench the reaction. The aqueous layer was separated and extrated with EtOAc (30 mL x 2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. The crude residue was dissolved in dry DCM (50 mL) and MnO_2 (8.7 g, 100.1 mmol) was added in one portion. The mixture was then reacted at room temperature for 10 h. After reaction was complete, the reaction mixture was filtrated with celite and concentrated to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:2) followed by EtOAc/*n*-hexane (1:1) to afford atropisomeric mixture aldehyde **23a** (3.7 g, 96% yield over 2 steps) as a white solid: mp = 123–125 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3057, 2968, 2935, 2841, 2753, 1762, 1697, 1628, 1605, 1498, 1458, 1429, 1317, 1201, 1153; ^1H NMR ($CDCl_3$, 400 MHz), major one: δ 0.72 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H), 2.10 (s, 3H), 2.80 (sext, J = 6.8 Hz, 1H), 2.91 (sext, J = 6.8 Hz, 1H), 3.33 (sext, 6.8 Hz, 1H), 3.65 (s, 3H), 3.76 (sext, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.89 (s, 3H), 6.31 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), major one: δ 11.7, 13.7, 20.8, 37.9, 42.0, 54.9, 55.2, 55.5, 95.3, 105.8, 110.0, 119.2, 124.1, 133.8, 134.2, 137.9, 140.5, 157.4, 159.2, 160.1, 167.1, 190.7; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{22}H_{28}NO_5$ 386.1962, found: 386.1962.

2',4'-Bis(benzyloxy)-*N*,*N*-diethyl-3-formyl-5-methoxy-6'-methyl-[1,1'-biphenyl]-2-carboxamide (23b). According to the synthetic procedures similar to compound **23a**, atropisomeric mixture aldehyde **23b** (5.1 g, 93% yield over 2 steps) was prepared from lactone **10b** (4.7 g, 10.1 mmol) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3032, 2970, 2933, 2870, 2753, 1696, 1627, 1603, 1498, 1455, 1430, 1394, 1380, 1317, 1278, 1153; ^1H NMR ($CDCl_3$, 400 MHz), major one: δ 0.69-0.75 (m, 6H), 2.14 (s, 3H), 2.64 (sext, J = 7.2 Hz, 1H), 2.89 (sext, J = 6.4 Hz, 1H), 3.20 (sext, J = 7.2 Hz,

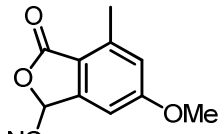
1H), 3.70 (sext, J = 6.4 Hz, 1H), 3.89 (s, 3H), 4.86 (d, J = 12.4 Hz, 1H), 4.98 (d, J = 12.4, 1H), 5.05 (s, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.10-7.12 (m, 2H), 7.25-7.45 (m, 8H), 7.48 (d, J = 2.4 Hz, 1H), 10.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), major one: δ 11.8, 13.5, 20.9, 37.9, 42.3, 55.5, 69.6, 70.0, 97.5, 107.4, 110.3, 119.9, 124.0, 126.4, 127.4, 127.6, 127.9, 128.4, 128.5, 133.8, 134.3, 136.5, 136.8, 137.7, 140.7, 156.4, 159.2, 159.3, 167.0, 190.8; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{34}H_{36}NO_5$ 538.2588, found: 538.2591.

4-(Benzyloxy)-*N*,*N*-diethyl-2-formyl-6-methylbenzamide (23d). According to the synthetic procedures similar to compound **23a**, aldehyde **23d** (2.3 g, 72% yield over 2 steps) was prepared from lactone **10d** (2.5 g, 9.8 mmol) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3034, 2976, 2935, 2873, 2750, 1698, 1629, 1603, 1455, 1317, 1286, 1150; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 3.06-3.13 (m, 2H), 3.53-3.60 (m, 1H), 3.68-3.75 (m, 1H), 5.11 (s, 2H), 7.09 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.35-7.45 (m, 5H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.5, 13.7, 18.5, 38.9, 42.6, 70.1, 110.9, 123.4, 127.4, 128.1, 128.6, 132.7, 133.6, 136.0, 136.8, 158.6, 168.0, 190.4; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{20}H_{24}NO_3$ 326.1756, found: 326.1748.

4-(2,4-Dimethoxy-6-methylphenyl)-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (24a). To a stirred solution of aldehyde **23a** (1.9 g, 4.9 mmol) in dry DCM (10 mL) was added cat. 18-crown-6 (132 mg, 0.50 mmol), cat. KCN (33 mg, 0.50 mmol) and TMSCN (744 mg, 7.50 mmol) at 0 □. The resulting solution was stirred at room temperature under N_2 for 2 h and then DCM was evaporated to give the crude residue, which was dissolved in HOAc (15 mL) and reacted at 60 □ under N_2 for 15 h. After reaction was complete, HOAc was evaporated under reduced pressure to give the crude residue, which was recrystallized from diethyl ether and *n*-hexane to afford diasteromeric mixture cyanophthalide **24a** (1.5 g, 87% yield) as a white solid: mp = 179–183 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3060, 3003, 2941, 2841, 1786, 1608, 1586, 1480, 1466, 1439, 1346, 1320, 1268, 1211, 1154; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 1.8H), 2.08 (s, 1.2H), 3.65 (s, 1.2H), 3.69 (s, 1.8 H), 3.84 (s, 3H), 3.95 (s, 3H), 5.97 (s, 1H), 6.40 (d, J = 2.0 Hz, 0.4H), 6.41 (d, J = 2.4 Hz, 0.6H), 6.44 (d, J = 2.4 Hz, 0.6H), 6.46 (d, J = 2.0 Hz, 0.4H), 6.95 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2, 20.3, 55.1, 55.5, 56.0, 64.2, 95.8, 95.9, 105.3, 106.4, 106.4, 114.5, 114.8, 114.8, 116.7, 116.7, 121.1, 137.6, 137.7, 140.3, 140.4, 144.9, 145.0, 157.7, 157.7, 160.5, 165.0, 165.9, 166.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{19}H_{17}NO_5Na$ 362.0999, found: 362.1003.

4-(2,4-Bis(benzyloxy)-6-methylphenyl)-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (24b). According to the synthetic procedures similar to compound **24a**, diasteromeric mixture cyanophthalide **24b** (1.8 g, 75% yield) was prepared from

aldehyde **23b** (2.7 g, 5.0 mmol) as a white solid: mp = 66–70 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3033, 2929, 2870, 1787, 1607, 1588, 1480, 1455, 1346, 1320, 1213, 1155; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.07 (1.8H), 2.10 (s, 1.2H), 3.91 (s, 1.8H), 3.92 (s, 1.2H), 4.89 (d, J = 12.4 Hz, 0.6H), 4.93 (d, J = 12.4 Hz, 0.6H), 4.94 (s, 0.8H), 5.05 (s, 0.8H), 5.06 (s, 1.2H), 5.84 (s, 0.4H), 5.94 (s, 0.6H), 6.53-6.57 (m, 2H), 6.95-7.46 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 56.0, 56.1, 64.2, 64.2, 70.0, 70.3, 98.1, 98.3, 105.3, 105.3, 107.9, 107.9, 114.4, 114.5, 115.1, 117.6, 121.1, 121.1, 126.7, 126.9, 127.6, 127.6, 127.7, 128.0, 128.2, 128.4, 128.6, 136.5, 136.7, 136.8, 137.6, 137.9, 140.4, 140.5, 144.8, 144.8, 156.9, 157.0, 159.7, 159.8, 165.0, 165.0, 166.0, 166.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{31}H_{25}NO_5Na$ 514.1625, found: 514.1625.



24c

1,3-dihydro-6-methoxy-4-methyl-3-oxoisobenzofuran-1-carbonitrile (24c). According to the synthetic procedures similar to compound **24a**, cyanophthalide **24c** (1.7 g, 83% yield over 3 steps) was prepared from lactone **10c** (1.8 g, 10.1 mmol) as a white solid: mp = 164.0–165.5 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3050, 2945, 1760, 1619, 1589, 1489, 1319, 1148, 1011; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.65 (s, 3H), 3.93 (s, 3H), 5.94 (s, 1H), 6.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 56.1, 64.6, 104.3, 114.2, 114.3, 119.6, 142.5, 145.0, 165.3, 167.3; HRMS (EI) m/z: [M] calcd. for $C_{11}H_9NO_3$: 203.0582, found: 203.0581.

6-(Benzyloxy)-4-methyl-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (24d). According to the synthetic procedures similar to compound **24a**, cyanophthalide **24d** (1.3 g, 95% yield) was prepared from aldehyde **23d** (1.6 g, 4.9 mmol) as a white solid: mp = 168–169 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3092, 3065, 3035, 2930, 1776, 1613, 1596, 1347, 1314, 1150; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.64 (s, 3H), 5.15 (d, J = 11.6 Hz, 1H), 5.20 (d, J = 11.6 Hz, 1H), 5.92 (s, 1H), 6.99 (s, 1H), 7.01 (s, 1H), 7.38-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.4, 64.5, 70.7, 105.1, 114.2, 114.4, 120.3, 127.5, 128.5, 128.8, 135.2, 142.5, 144.9, 164.3, 167.3; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{17}H_{14}NO_3$ 280.0968, found: 280.0968.

Tetarimycin A (1). To a stirred solution of enone **9a** (192 mg, 0.50 mmol) and benzyl-protecting cyanophthalide **24d** (140 mg, 0.50 mmol) in dry THF (2.4 mL) at 0 □ was added LiHMDS solution (1 M in THF, 0.6 mL) via syringe under argon. The resulting orange solution was stired at room temperature for 2 h (The orange solution became dark orange). Saturated NH_4Cl solution (5 mL) was added to quench the reaction at 0 □ under argon. The aqueous layer was separated and extracted with

EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to 10 mL, in which methanol (1 mL) and 10% wt Pd/C (100 mg) were added, and then stirred at room temperature under H_2 (1 atm) for 15 h. The reaction mixture was diluted with EtOAc (20 mL), filtrated with celite and concentrated to give the crude residue, which without purification was dissolved in EtOAc (10 mL) and treated with DDQ (114 mg, 0.50 mmol) and stirred at room temperature for 1 h. Saturated $NaHCO_{3(aq)}$ (5 mL) was added to quench the reaction and extracted with EtOAc (20 mL). The organic extract was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with DCM followed by EtOAc/DCM (2:1) to afford tetarimycin A (**1**) (115 mg, 67% yield over 3 steps) as an orange solid:[4e] mp > 300 □, decomp.; IR (KBr, cm^{-1}) ν_{max} 3441, 3368 (br), 3032, 2984, 2928, 1671, 1630, 1612, 1583, 1560, 1463, 1326, 1276, 1215, 1150; ^{1}H NMR (d_6-Acetone, 400 MHz): δ 1.82 (s, 6H), 2.61 (s, 3H), 6.31 (d, J =2.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 2.8 Hz, 1H), 9.65 (br s, 2H), 13.03 (s, 1H); ^{13}C NMR (d_6-Acetone, 100 MHz): δ 21.6, 30.0, 39.9, 101.8, 106.3, 110.7, 111.9, 124.7, 124.9, 136.8, 137.6, 143.2, 155.6, 156.1, 161.8, 165.9, 166.0, 183.8, 186.5, 186.5; HRMS (EI) m/z: [M] calcd. for $C_{21}H_{16}O_6$ 364.0947, found: 364.0950.

(±)-Naphthacemycin A_9 (6). According to the synthetic procedures similar to compound **1**, compound **6** (293 mg, 57% yield over 3 steps) was prepared from enone **9a** (384 mg, 1.00 mmol) and cyanophthalide **24a** (339 mg, 1.00 mmol) as a dark orange solid:[4f, 6b] mp = 126–127 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3364 (br), 3060, 2939, 2840, 1674, 1633, 1608, 1582, 1497, 1464, 1456, 1313, 1200, 1152; ^{1}H NMR (d_4-MeOH, 400 MHz): δ 1.79 (s, 3H), 1.85 (s, 3H), 2.05 (s, 3H), 3.61 (s, 3H), 3.84 (s, 3H), 3.95 (s, 3H), 6.22 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H); ^{13}C NMR (d_4-MeOH, 100 MHz): δ 21.0, 30.2, 30.7, 40.5, 55.9, 56.2, 56.6, 97.3, 102.1, 106.8, 108.1, 110.5, 110.6, 122.7, 125.5, 127.5, 136.9, 137.4, 138.3, 141.5, 156.5, 157.3, 158.4, 161.7, 164.3, 166.5, 167.2, 184.3, 186.5, 187.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{30}H_{26}O_8Na$ 537.1520, found: 537.1520.

2,4,9-Trimethoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (26). According to the synthetic procedures similar to compound **1**, but without hydrogenolysis, compound **26** (146 mg, 72% yield over 2 steps) was prepared from enone **S5** (116 mg, 0.50 mmol) and cyanophthalide **24c** (102 mg, 0.50 mmol) as an orange solid: mp = 216–218 ^{o}C; IR (KBr, cm^{-1}) ν_{max} 3314 (br), 3084, 2982, 2949, 2848, 1677, 1632, 1608, 1586, 1459, 1305, 1159; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.80 (s, 6H), 2.73 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 6.42 (d, J = 2.0 Hz, 1H), 6.66 (d, J = 2.0 Hz,

1H) 7.01 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 29.1, 38.9, 55.4, 55.7, 56.0, 96.9, 102.3, 108.9, 116.2, 123.6, 123.9, 136.4, 138.7, 143.5, 150.4, 154.9, 161.4, 162.5, 164.3, 181.5, 183.4, 185.9; HRMS (EI) m/z: [M] calcd. for $C_{24}H_{22}O_6$ 406.1416, found: 406.1421.

2,4-dihydroxy-9-methoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (28). According to the synthetic procedures similar to compound **1**, compound **28** (123 mg, 65% yield over 3 steps) was prepared from enone **9a** (192 mg, 0.50 mmol) and cyanophthalide **24c** (102 mg, 0.50 mmol) as an orange solid: mp > 300 □, decomp.; IR (KBr, cm^{-1}) ν_{max} 3314 (br), 3084, 3011, 2982, 2949, 2848, 1677, 1632, 1608, 1586, 1346, 1305, 1235, 1158; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 1.73 (s, 6H), 2.60 (s, 3H), 3.92 (s, 3H), 6.24 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 12.96 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 21.0, 29.4, 38.6, 55.8, 100.7, 105.6, 108.8, 109.0, 123.0, 124.3, 135.2, 135.9, 141.5, 154.4, 154.7, 162.0, 164.1, 165.3, 182.9, 184.8, 185.1; HRMS (EI) m/z: [M] calcd. for $C_{22}H_{18}O_6$ 378.1103, found: 378.1090.

9-Hydroxy-2,4-dimethoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (29). According to the synthetic procedures similar to compound **1**, compound **29** (137 mg, 70% yield over 3 steps) was prepared from enone **S5** (116 mg, 0.50 mmol) and cyanophthalide **24d** (140 mg, 0.50 mmol) as an orange solid: mp > 300 □, decomp.; IR (KBr, cm^{-1}) ν_{max} 3272 (br), 3004, 2971, 2941, 2841, 1674, 1612, 1596, 1570, 1464, 1325, 1207; ^{1}H NMR (d_6-DMSO): *δ* 1.74 (s, 6H), 2.57 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 6.60 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 10.90 (br s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): *δ* 21.5, 28.7, 38.5, 55.7, 55.9, 97.4, 102.9, 111.3, 115.2, 122.1, 123.8, 136.2, 138.4, 142.4, 149.7, 154.7, 160.4, 161.3, 164.0, 180.2, 183.0, 185.4; HRMS (EI) m/z: [M] calcd. for $C_{23}H_{20}O_6$ 392.1260, found: 392.1244.

2,9-Dihydroxy-4-methoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (30). According to the synthetic procedures similar to compound **1**, compound **30** (142 mg, 75% yield over 3 steps) was prepared from enone **S7** (154 mg, 0.50 mmol) and cyanophthalide **24d** (140 mg, 0.50 mmol) as an orange solid: mp > 300 □; IR (KBr, cm^{-1}) ν_{max} 3297 (br), 2980, 2932, 2851, 1681, 1592, 1460, 1323, 1260; ^{1}H NMR (d_6-DMSO, 400 MHz): *δ* 1.69 (s, 6H), 2.56 (s, 3H), 3.78 (s, 3H), 6.44 (d, *J* = 2.0 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 10.52 (br s, 1H), 10.82 (br s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): *δ* 21.6, 28.9, 38.2, 55.7, 98.2, 104.5, 111.3, 114.1, 122.2, 123.8, 136.2, 138.7, 142.4, 149.4, 154.8, 160.8, 161.2, 162.9, 180.0, 183.2, 185.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{18}O_6Na$ 401.0996, found: 401.0996.

2,9-Dihydroxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (31). According to the synthetic procedures similar to compound **1**, compound **31** (103 mg, 59% yield over 3 steps) was prepared from enone **S8** (139 mg, 0.50 mmol) and cyanophthalide **24d** (140 mg, 0.50 mmol) as an orange solid: mp > 300 □; IR (KBr, cm^{-1}) ν_{max} 3321 (br), 2982, 2933, 2729, 1669, 1609, 1594, 1568, 1464, 1324, 1304, 1264, 1244, 1118; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 1.73 (s, 6H), 2.56 (s, 3H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 6.99 (d, 2.4 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 10.71 (br s, 2H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 21.2, 28.8, 38.0, 111.0, 112.0, 115.7, 122.8, 123.0, 123.8, 128.6, 135.8, 136.2, 141.9, 152.9, 153.4, 161.1, 162.7, 180.6, 183.4, 186.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{21}H_{16}O_5Na$ 371.0890, found: 371.0890.

2-Hydroxy-9-methoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (32). According to the synthetic procedures similar to compound **1**, compound **32** (127 mg, 70% yield over 3 steps) was prepared from enone **S8** (139 mg, 0.50 mmol) and cyanophthalide **24c** (102 mg, 0.50 mmol) as an orange solid: mp = 258–259 □; IR (KBr, cm^{-1}) ν_{max} 3248 (br), 3079, 2976, 2939, 2838, 1677, 1604, 1581, 1563, 1477, 1306, 1230, 1120, 1078, 1052; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 1.74 (s, 6H), 2.60 (s, 3H), 3.91 (s, 3H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 10.58 (br s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 21.1, 28.8, 38.0, 55.8, 108.9, 112.0, 115.8, 122.9, 123.0, 124.1, 128.6, 135.7, 136.0, 141.7, 153.1, 153.4, 162.0, 162.7, 180.4, 183.6, 185.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{18}O_5Na$ 385.1046, found: 385.1045.

1-Chloro-2,4,9-trihydroxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (34). According to the synthetic procedures similar to compound **1** with hydrogenolysis carried out for 2 h instead, compound **34** (115 mg, 58% yield over 3 steps) was prepared from enone **9b** (209 mg, 0.50 mmol) and cyanophthalide **24d** (140 mg, 0.50 mmol) as an orange solid: mp > 300 □; IR (KBr, cm^{-1}) ν_{max} 3441 (br), 2926, 1669, 1633, 1614, 1575, 1564, 1423, 1398, 1361, 1314, 1263, 1212, 1137, 1122; ^{1}H NMR (d_6-DMSO, 400 MHz): δ 1.96 (s, 6H), 2.55 (s, 3H), 6.53 (s, 1H), 7.01 (d, J = 2.8 Hz, 1H), 7.24 (d, J = 2.8 Hz, 1H), 10.81 (br s, 1H), 13.48 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 21.2, 24.6, 38.9, 102.1, 109.8, 110.6, 111.2, 123.0, 123.9, 132.6, 136.3, 141.9, 149.4, 155.9, 161.2, 161.8, 163.0, 182.5, 184.9, 186.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{21}H_{15}ClO_6Na$ 421.0449, found: 421.0451.

Compound 35 (a mixture of hemiketal and *p*-quinone, HK/Q)[23] According to the synthetic procedures similar to compound **1**, compound **35** (186 mg, 55% yield over 3 steps) was prepared from enone **9a** (269 mg, 0.70 mmol) and cyanophthalide **24b** (344 mg, 0.70 mmol) as a yellow solid: mp > 300 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3336

(br), 3019, 2976, 2939, 2838, 1673, 1644, 1619, 1587, 1486, 1465, 1408, 1352, 1313, 1236, 1163, 1145; ^{1}H NMR (d_6-Acetone, 400 MHz), HK:Q = 6.5/1, hemiketal (HK)**:** δ 1.81 (s, 3H), 1.84 (s, 3H), 2.72 (s, 3H), 3.97 (s, 3H), 5.77 (br s, 1H), 6.39 (d, J = 1.6 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 12.67 (s, 1H); quinone (Q): δ 1.82 (s, 3H), 1.85 (s, 3H), 1.96 (s, 3H), 3.99 (s, 3H), 6.30 (d, J = 1.6 Hz, 1H), 6.33 (s, 2H). 6.73 (d, J = 1.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 12.95 (s, 1H); ^{13}C NMR (d_6-Acetone, 100 MHz), hemiketal (HK): δ 23.0, 26.8, 32.3, 40.4, 56.1, 91.3, 101.9, 104.6, 106.6, 107.6, 110.3, 114.5, 115.2, 118.6, 126.0, 130.9, 132.7, 137.6, 140.5, 151.1, 153.7, 157.2, 159.3, 161.3, 166.0, 166.7, 185.2, 188.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{28}H_{22}O_8Na$ 509.1207, found: 509.1208.

4-Hydroxy-2,9-dimethoxy-7,12,12-trimethyltetracene-5,6,11(12H)-trione (27). To a stirred solution of tetracene **26** (106 mg, 0.26 mmol) in dry MeCN (2.5 mL) was added TMSI (520 mg, 2.6 mmol) dropwise at 0 □ under argon. The reaction mixture was stirred at room temperature under argon for 15 h. After reaction was complete, water was added to quench reaction at 0 □. After MeCN was vaporated, EtOAc (20 mL) was added to extract the aqueous layer. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with DCM/*n*-hexane (2:1) followed by DCM to afford compound **27** (45 mg, 44% yield) as an orange solid: mp = 204–206 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3419 (br), 2975, 2937, 1673, 1633, 1609, 1573, 1301; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.81 (s, 6H), 2.72 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 6.41 (d, J = 2.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 2.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 13.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8, 29.9, 39.1, 55.6, 55.7, 98.7, 105.2, 108.7, 110.3, 123.7, 124.6, 135.1, 136.2, 142.9, 153.9, 155.3, 162.5, 165.4, 166.3, 183.5, 185.6, 185.6; HRMS (EI) m/z: [M] calcd. for $C_{23}H_{20}O_6$ 392.1260, found: 392.1243.

5,5,10-Trimethyl-6,11,12-trioxo-5,6,11,12-tetrahydrotetracene-1,3,8-triyl triacetate (33). To a stirred solution of tetarimycin A (**1**) (146 mg, 0.40 mmol) in dry pyridine (3 mL) at 0 □ was added Ac_2O (412 mg, 381 μL, 4.00 mmol) under N_2. The reaction mixture was stirred at 50 □ under N_2 for 3 h. After reaction was complete, water was added to quench reaction at 0 □. Then the reaction mixture was extracted with EtOAc (10 mL x 2). The combined organic layer was washed with 5% $HCl_{(aq)}$, water and brine, dried over $MgSO_4$, filtered and concentrated to afford compound **33** (190 mg, 97% yield) as a yellow solid: mp = 201–203 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2959, 2935, 2867, 1587, 1458, 1430, 1362, 1314, 1209, 1154, 1054; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (s, 6H), 2.34 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 2.76 (s, 3H), 6.93 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 7.72 (d, J = 2.4 Hz,

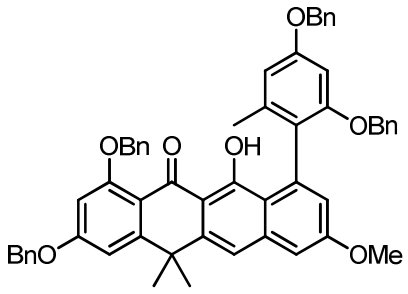
1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 21.1, 22.0, 29.1, 38.8, 116.3, 117.3, 118.3, 121.3, 127.8, 130.6, 135.7, 136.3, 143.1, 150.6, 152.4, 153.5, 153.6, 154.4, 168.0, 168.6, 169.5, 180.1, 183.1, 184.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{22}O_9Na$ 513.1156, found: 513.1172.

Ethyl 2-(2-ethoxy-2-oxoethyl)-4,6-dimethoxybenzoate (36). To a stirred solution of **16b** (8.4 g, 48.8 mmol) and sodium hydride (60%, 5.0 g, 125.0 mmol) in dry THF (100 mL) at 0 □ was slowly added diethyl malonate (16.0 g, 100.0 mmol) under N_2. After the mixture was stired at 0 □ for 30 min, LDA (2.0 M, 25 mL,50 mmol) was added over 2 h, keeping the temperature below 5 □. The reaction mixture was slowly added to a stirred solution of 5% aqueous HCl (200 mL) at 0 □. EtOAc (50 mL x 2) was added to extract the aqueous layer. The organic portions were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford diethyl homophthalate **36** (6.6 g, 46% yield) as a colorless oil:[20] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 3.66 (s, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 6.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 17.4, 19.0, 30.8, 64.5, 68.7, 104.7, 113.8, 114.3, 119.9, 142.3, 145.0, 164.9, 167.4.

Ethyl 2-(2-ethoxy-2-oxoethyl)-6-hydroxy-4-methoxybenzoate (37). To a stirred solution of **36** (6.4 g, 21.5 mmol) in dry DCM (100 mL) at 0 □ was added BCl_3 (1M in DCM, 23 mL, 23 mmol) under N_2. After stirring at room temperature for 5 h, reaction was quenched with ice water at 0 □. The organic portion was washed with sat. $NaHCO_{3(aq)}$ and water, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized from diethyl ether and *n*-hexane to afford phenol **37** (5.4 g, 89% yield) as white solid:[24] mp = 63–65 □; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 3.81 (s, 3H), 3.86 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 6.28 (d, J = 2.2 Hz, 1H), 6.42 (d, J = 2.2, 1H), 11.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 14.1, 42.8, 55.3, 60.6, 61.4, 100.0, 105.2, 112.5, 138.0, 163.8, 165.6, 170.8, 171.3.

2,4-Bis(benzyloxy)-7-(2,4-bis(benzyloxy)-6-methylphenyl)-1-chloro-6-hydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (40). To a stirred solution of **9b** (209 mg, 0.50 mmol) and **39b** (284 mg, 0.50 mmol) in dry THF (2.4 mL) at 0 □ was added LiHMDS (1 M in THF, 0.6 mL) under N_2. The mixture was then allowed to react at room temperature under N_2 for 3 h. After reaction was complete, $KOH_{(aq)}$ (2 N, 1 mL) and MeOH (3 mL) were added sequentially to facilitate basic hydrolysis. The resulting mixture was stirred at room temperature under N_2 for 24 h. After reaction was complete, solvent was evaporated and resulting aqueous solution was neutralized to pH~4 with 5% $HCl_{(aq)}$ and then extracted with EtOAc (20 mL x 2). The combined

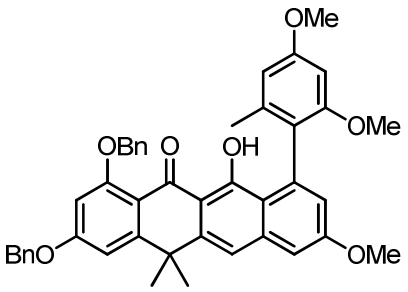
organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the corresponding acid intermediate. To a stirred solution of the acid intermediate in dry toluene (5 mL) was added DBU (381 mg, 2.50 mmol) under N_2. The resulting mixture was heated to reflux for 4 h. After reaction was complete, 5% $HCl_{(aq)}$ (5 mL) was added to quench the reaction. The separated organic layer was diluted with EtOAc (10 mL), washed with water, dried over $MgSO_4$ and filtered to give the solution, which in turn was added DDQ (114 mg, 0.50 mmol) in one portion. The mixture was then allowed to react at room temperature under N_2 for 1 h. After reaction was complete, sat. $NaHCO_{3(aq)}$ was added to quench the reaction. The separated organic layer was washed with water and brine, dried over $MgSO_4$ and filtered to give the crude residue, which was purified by chromatography on silical gel to afford compound **40** (152 mg, 35% over 4 steps) as a yellow solid: mp = 110–112 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3064, 3031, 2933, 2870, 1608, 1576, 1498, 1454, 1402, 1381, 1306, 1258, 1196, 1173, 1041, 1028; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.08 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 3.95 (s, 3H), 4.93 (s, 2H). 5.06 (d, J = 11.4 Hz, 1H), 5.09 (d, J = 11.4 Hz, 1H), 5.14 (s, 2H), 5.17 (s, 2H), 6.51 (d, J = 2.4 Hz, 1H), 6.8 (d, J = 2.4 Hz, 1H), 6.66 (s, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.93 (s, 1H), 6.94 (d, J = 2.4 Hz, 1H), 7.03-7.08 (m, 4H), 7.29-7.53 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8, 30.0, 30.3, 39.7, 55.2, 70.0, 70.2, 71.0, 71.7, 98.3, 99.7, 105.5, 107.2, 107.7, 114.5, 114.7, 115.7, 117.4, 120.7, 126.5, 127.0, 127.0, 127.0, 127.8, 127.9, 127.9, 128.0, 128.3, 128.5, 128.7, 128.8, 135.6, 136.3, 137.0, 137.2, 137.5, 138.7, 140.7, 148.1, 149.8, 156.7, 158.3, 159.0, 159.9, 160.5, 165.2, 187.3; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{56}H_{48}ClO_7$ 867.3083, found: 867.3081.



46

2,4-Bis(benzyloxy)-7-(2,4-bis(benzyloxy)-6-methylphenyl)-6-hydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (46). According to the synthetic procedures similar to compound **40**, compound **46** (192 mg, 46% yield over 4 steps) was prepared from enone **9a** (192 mg, 0.50 mmol) and diethyl homophthalide **39b** (284 mg, 0.50 mmol) as a yellow solid: mp = 89–90 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3063, 3032, 2964, 2928, 2862, 1598, 1498, 1454, 1426, 1398, 1378, 1296, 1263, 1153; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.72 (s, 3H), 1.75 (s, 3H), 2.08 (s, 3H), 3.94 (s, 3H), 4.93 (s,

2H), 5.06 (d, J = 11.2 Hz, 1H), 5.09 (d, J = 11.2 Hz, 1H), 5.14 (s, 2H), 5.18 (s, 2H), 6.51 (d, J = 2.4 Hz, Hz, 1H), 6.58 (d, J = 2.4 Hz, 2H), 6.82 (d, J = 2.8 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.93 (s, 1H), 6.95 (d, J = 2.4 Hz, 1H), 7.02-7.04 (m ,4H), 7.30-7.61 (m, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 33.5, 34.2, 38.9, 55.1, 69.9, 70.0, 70.7, 98.2, 99.0, 104.6, 105.8, 107.1, 109.2, 113.3, 114.0, 117.9, 120.5, 126.4, 126.5, 126.9, 127.5, 127.5, 127.7, 127.8, 127.9, 128.2, 128.4, 128.4, 128.6, 135.8, 136.4, 136.9, 137.1, 137.4, 138.6, 140.0, 144.7, 155.1, 156.5, 158.2, 159.7, 161.9, 163.1, 165.5, 187.6; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{56}H_{49}O_7$ 833.3473, found: 833.3470.



47

2,4-Bis(benzyloxy)-7-(2,4-dimethoxy-6-methylphenyl)-6-hydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (47). According to the synthetic procedures similar to compound **40**, compound **47** (92 mg, 27% yield over 4 steps) was prepared from enone **9a** (192 mg, 0.50 mmol) and diethyl homophthalide **39a** (208 mg, 0.50 mmol) as a yellow solid: mp = 98–99 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2924, 2853, 1598, 1498, 1454, 1426, 1398, 1377, 1319, 1296, 1200, 1152; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71 (s, 3H), 1.74 (s, 3H), 1.99 (s, 3H), 3.64 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 5.13 (s, 2H), 5.18 (s, 2H), 6.43 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 7.29 (s, 1H), 7.29-7.46 (m, 8H), 7.59 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6, 33.6, 34.3, 39.0, 55.1, 55.2, 55.8, 70.1, 70.8, 95.8, 99.1, 104.7, 105.5, 105.7, 109.2, 113.4, 114.1, 117.8, 120.5, 125.6, 126.6, 127.6, 127.6, 128.3, 128.5, 128.7, 135.9, 136.5, 137.1, 138.7, 140.1, 144.8, 155.2, 157.6, 159.0, 159.7, 161.9, 163.2, 165.6, 187.6; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{44}H_{41}O_7$ 681.2847, found: 681.2846.

(±)-Fasamycin A (2). To a stirred solution of compound **40** (174 mg, 0.20 mmol) in dry DCM (2 mL) at -78 □ was added BBr_3 (251 mg, 95 μL, 1.00 mmol) under N_2. The mixture was then allowed to react at room temperature under N_2 for 5 h. After reaction was complete, ice water (5 mL) was added to quench the reaction. DCM was then evaporated to give the crude residue, which was extracted with EtOAc (20 mL). The organic portion was was washed with sat. $NaHCO_{3(aq)}$ and brine, dried over

$MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford (±)-fasamycin A (75 mg, 76%) as a yellow solid:[4d] mp > 300 □; IR (KBr, cm^{-1}) ν_{max} 3412 (br), 2979, 2937, 1702, 1606, 1594, 1560, 1453, 1398, 1384, 1338, 1251, 1183, 1160, 1112; ^1H NMR (d_4-MeOH, 400 MHz): δ 1.88 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 6.23 (d, J = 2.4 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.44 (s, 1H), 6.71 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.34 (s, 1H); ^{13}C NMR (d_4-MeOH, 100 MHz): δ 20.8, 30.3, 30.4, 40.8, 101.0, 103.7, 106.4, 108.9, 109.6, 110.1, 113.5, 117.1, 117.9, 122.8, 124.5, 138.4, 141.0, 143.6, 149.3, 150.1, 155.6, 157.6, 160.4, 163.0, 165.6, 166.7, 191.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{27}H_{21}ClO_7Na$ 515.0868, found: 515.0865.

1-Chloro-7-(2,4-dihydroxy-6-methylphenyl)-2,4,6-trihydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (41). To a stirred solution of compound **40** (174 mg, 0.20 mmol) in dry DCM (2 mL) at -78 □ was added BBr_3 (251 mg, 95 μL, 1.00 mmol) under N_2. The mixture was then allowed to react at -40 □ under N_2 for 10 mins. After reaction was complete, ice water (5 mL) was added to quench the reaction. DCM was then evaporated to give the crude residue, which was extracted with EtOAc (20 mL). The organic layer was washed with sat. $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford compound **41** (94 mg, 93% yield) as a yellow solid: mp = 143–145 □; IR (KBr, cm^{-1}) ν_{max} 3307 (br), 2924, 2853, 2734, 1704, 1608, 1594, 1558, 1455, 1397, 1372, 1336, 1253, 1201, 1172, 1151; ^1H NMR (d_4-MeOH, 400 MHz): δ 1.87 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 3.97 (s, 3H), 6.23 (d, J = 2.4 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.46 (s, 1H), 6.75 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.50 (s, 1H); ^{13}C NMR (d_4-MeOH, 100 MHz): δ 20.9, 30.3, 30.4, 40.9, 56.0, 100.9, 103.7, 106.9, 106.9, 108.9, 109.7, 113.5, 117.8, 118.5, 122.9, 124.3, 138.4, 140.5, 143.4, 149.6, 150.1, 155.6, 157.7, 162.3, 162.9, 165.6, 166.3, 191.8; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{28}H_{24}ClO_7$ 507.1205, found: 507.1204.

7-(2,4-Dihydroxy-6-methylphenyl)-2,4,6-trihydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (42). To a stirred solution of compound **46** (167 mg, 0.20 mmol) in MeOH/EtOAc (1 mL/5 mL) was added 10% wet Pd/C (50 mg). The mixture was then allowed to react at room temperature under 1 atm. H_2 for 15 h. After the reaction was complete, it was filtrated with celite and concentrated to afford **42** (94 mg, 99% yield) as a bright yellow solid: mp = 211–213 □; IR (KBr, cm^{-1}) ν_{max} 3422 (br), 3278 (br), 2980, 2927, 2857, 1693, 1614, 1601, 1460, 1375, 1342, 1276, 1200, 1166, 1148; ^1H NMR (d_4-MeOH, 400 MHz): δ 1.72 (s, 3H), 1.74 (s, 3H), 1.87 (s, 3H), 3.97 (s, 3H), 6.21 (d, J = 2.4 Hz, 1H), 6.23 (d, J = 2.0 Hz, 1H), 6.26 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 7.52 (s, 1H); ^{13}C NMR (d_4-MeOH, 100 MHz): δ 20.9, 34.6, 34.8, 39.8, 56.0, 100.9, 102.2, 107.1, 107.1,

108.2, 108.7, 108.9, 116.9, 118.8, 122.7, 124.4, 138.5, 140.3, 142.8, 146.9, 155.5, 155.9, 157.5, 162.0, 166.5, 166.6, 166.7, 191.8; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{28}H_{25}O_7$ 473.1595, found: 473.1594.

7-(2,4-Dimethoxy-6-methylphenyl)-2,4,6-trihydroxy-9-methoxy-12,12-dimethyltetracen-5(12H)-one (44). According to the synthetic procedures similar to compound **42**, compound **44** (97 mg, 97% yield) was prepared from compound **47** (136 mg, 0.20 mmol) as a bright yellow solid: mp = 144–146 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3356 (br), 2964, 2932, 2839, 1604, 1466, 1431, 1398, 1319, 1279, 1200, 1150, 1028; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.70 (s, 3H), 1.71 (s, 3H), 1.99 (s, 3H), 3.65 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 5.41 (br s, 1H), 6.25 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 7.33 (s, 1H), 13.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 33.3, 34.7, 38.6, 55.3, 55.3, 56.1, 96.2, 101.4, 105.4, 106.0, 106.1, 107.3, 108.4, 115.1, 117.4, 120.9, 125.5, 137.2, 138.8, 140.9, 145.4, 154.3, 157.3, 159.1, 160.3, 162.7, 165.1, 165.5, 190.1; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{30}H_{29}O_7$ 501.1908, found: 501.1907.

Ethyl 1-(2,4-dihydroxy-6-methylphenyl)-8,10,12-trihydroxy-3-methoxy-6,6-dimethyl-11-oxo-6,11-dihydrotetracene-5-carboxylate (43). To a stirred solution of **9a** (192 mg, 0.50 mmol) and **39b** (284 mg, 0.50 mmol) in dry THF (2.4 mL) at 0 □ was added LiHMDS (1 M in THF, 0.6 mL) under N_2. The mixture was then allowed to react at room temperature under N_2 for 3 h. After the reaction was complete, sat. $NH_4Cl_{(aq)}$ (5 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc (20 mL). The organic portions were combined, washed with water and brine, dried over $MgSO_4$, filtered to give the solution of crude residue, which was added DDQ (114 mg, 0.50 mmol). The mixture was then allowed to react at room temperature under N_2 for 1 h. After reaction was complete, sat. $NaHCO_{3(aq)}$ was added to quench the reaction. The separated organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. To the solution of crude residue in MeOH/EtOAc (1 mL/5 mL), was added 10% wet Pd/C (50 mg). The mixture was then allowed to react at room temperature under 1 atm. H_2 for 15 h. After the reaction was complete, it was filtrated with celite and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford compound **43** (185 mg, 68% yield over 3 steps) as a yellow solid: mp = 126–128 □; IR (KBr, cm^{-1}) ν_{max} 3366 (br), 2977, 2937, 2865, 1702, 1602, 1465, 1403, 1349, 1319, 1257, 1205, 1186, 1153, 1030; ^1H NMR (d_4-MeOH, 400 MHz): δ 1.41 (t, J = 7.2 Hz, 3H), 1.74 (s, 3H), 1.75 (s, 3H), 1.87 (s, 3H), 3.86 (s, 3H), 4.47 (br s, 2H), 6.20 (d, J = 2.0 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H),

6.29 (d, J = 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H); ^{13}C NMR (d_4-MeOH, 100 MHz): δ 14.5, 20.9, 41.5, 55.9, 62.9, 101.0, 102.2, 104.7, 107.1, 107.5, 108.1, 109.0, 119.1, 122.2, 122.9, 124.5, 138.1, 139.4, 141.1, 143.2, 155.3, 156.7, 157.6, 162.4, 166.6, 166.9, 168.0, 173.6, 191.6; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{31}H_{29}O_9$ 545.1806, found: 545.1805.

7-(2,4-Dimethoxy-6-methylphenyl)-2,4-dihydroxy-6,9-dimethoxy-12,12-dimethyltetracen-5(12H)-one (45). To a stirred solution of compound **47** (136 mg, 0.20 mmol) in DMF (2 mL) was added Cs_2CO_3 (98 mg, 0.30 mmol) and MeI (43 mg, 0.30 mmol) under N_2. The mixture was then allowed to react at 50 □ under N_2 for 6 h. After the reaction was complete, water (5 mL) was added to quench the reaction. The resulting reaction mixture was extracted with EtOAc (20 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. To the solution of crude residue in MeOH/EtOAc (1 mL/5 mL) was added 10% wet Pd/C (50 mg). The mixture was then allowed to react at room temperature under 1 atm. H_2 for 15 h. After the reaction was complete, it was filtrated with celite and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford compound **45** (95 mg, 92% yield over 2 steps) as a yellow solid: mp = 115–117 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3349 (br), 2931, 2851, 1605, 1561, 1466, 1454, 1382, 1333, 1271, 1202, 1151, 1032; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71 (s, 3H), 1.74 (s, 3H), 1.98 (s, 3H), 3.35 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 6.27 (s, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.56 (s, 1H), 6.89 (d, J = 2.6 Hz, 1H), 7.11 (d, J = 2.6 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8, 33.9, 34.0, 38.7, 55.3, 55.3, 55.5, 62.1, 95.7, 101.4, 104.6, 105.4, 105.9, 110.6, 117.6, 120.4, 122.4, 123.2, 125.1, 137.2, 137.8, 140.1, 147.0, 153.1, 157.2, 158.9, 159.4, 161.9, 162.4, 165.5, 187.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{31}H_{30}O_7Na$ 537.1884, found: 537.1901.

As illustrated in Scheme S1, preparation of enones 9a and 9b via the first-generation route was demonstrated as follows:

Ethyl 4-(2,4-dimethoxyphenyl)butanoate (S1a). To a stirred solution of 1, 3-dimethoxybenzene **16a** (4.1 g, 29.6 mmol) and succinic anhydride (3.0 g, 30.0 mmol) in dry DCM (60 mL) was added $AlCl_3$ (4.0 g, 30.0 mmol) portionwise at 0 □. The mixture was then allowed to react at room temperature under N_2 for 15 h. After reaction was complete, ice water (30 mL) was added to quench the reaction. DCM was evaporated and then extracted with THF/EtOAc (40 mL/20 mL). The Organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was recrystallized from EtOAc and *n*-hexane to afford ketone acid (5.6 g, 80% yield). To a stirred solution of ketone acid (2.4 g, 10.1 mmol) in TFA (10 mL) was added Et_3SiH (5 mL) at 0 □, then reacted at room

temperature under N_2 for 6 h. After reaction was complete, TFA was evaporated under reducing pressure to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:4) followed by EtOAc/*n*-hexane (1:1) to afford saturated carboxyl acid (1.9 g, 86% yield). To a stirred solution of saturated carboxyl acid (1.5 g, 6.6 mmol) in DMF (7 mL) was added potassium carbonate (912 mg, 6.60 mmol) and ethyl iodide (1.2 g, 7.7 mmol) dropwise. The mixture was then allowed to react at room temperature under N_2 for 3 h. After reaction was complete, water (7 mL) was added to quench the reaction and then extracted with EtOAc (35 mL). Organic extract was washed with water (7 mL x 3) and brine, dried over $MgSO_4$, filtered and concentrated to obtain compound **S1a** (1.6 g, 96% yield) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2938, 2871, 2836, 1733, 1613, 1588, 1507, 1465, 1289, 1209, 1155, 1041; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J = 6.8 Hz, 3H), 1.88 (quin, J = 7.6 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 3.79 (s, 6H), 4.11 (q, J = 6.8 Hz, 2H), 6.40 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 2.4, 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 25.1, 28.7, 33.7, 55.0, 55.1, 59.9, 98.2, 103.6, 122.0, 130.0, 158.2, 159.1, 173.6; HRMS (EI) m/z: [M] calcd. for $C_{14}H_{20}O_4$ 252.1362, found: 252.1365.

Ethyl 4-(5-chloro-2,4-dimethoxyphenyl)butanoate (S1b). According to the synthetic procedures similar to compound **S1a**, ester **S1b** (5.3 g, 61% yield over 3 steps) was prepared from compound **16b** (5.2 g, 30.0 mmol) as a white solid: mp = 54–55 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2940, 2849, 1731, 1606, 1579, 1506, 1464, 1389, 1294, 1208, 1165, 1033; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 1.87 (quin, J = 7.6 Hz, 2H), 2.29 (t, J = 7.6 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 6.47 (s, 1H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 25.0, 28.6, 33.7, 55.6, 56.3, 60.2, 96.6, 112.9, 122.9, 130.7, 153.9), 156.9, 173.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{14}H_{19}ClO_4Na$ 309.0864, found: 309.0863.

5,7-Dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (S2a). To a stirred solution of ester **S1a** (2.0 g, 7.9 mmol) in dry THF (15 mL) was added MeMgBr solution (3 M in ether, 6 mL) dropwise at 0 □ under N_2. The mixture was then stirred at room temperature under N_2 for 1 h. After reaction was complete, ice water (10 mL) was added to quench the reaction at 0 □ and then the aqueous layer was extracted with EtOAc (30 mL x 2). The organic extract was washed with 5% $HCl_{(aq)}$, water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. The oil crude residue was slowly added to stirred PPA (5 mL) at room temperature. The mixture was then allowed to react at room temperature under N_2 for 2 h. After reaction was complete, ice water (10 mL) was added to quench the reaction and then extracted with EtOAc (30 mL). The organic extract was washed with water and brine,

dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:5) to afford tetralin **S2a** (1.6 g, 94% yield over 2 steps) as a colorless oil:[25] IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2933, 2864, 2854, 1608, 1590, 1462, 1320, 1270, 1210, 1141; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.27 (s, 6H), 1.58-1.63 (m, 2H), 1.73-1.79 (m, 2H), 2.56 (t, J = 6.8 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 6.28 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9, 23.4, 31.6, 34.0, 38.9, 55.1, 55.1, 95.0, 102.4, 117.5, 147.5, 157.7, 158.2.

8-Chloro-5,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (S2b). According to the synthetic procedures similar to compound **S2a**, tetralin **S2b** (1.5 g, 57% yield over 2 steps) was prepared from ester **S1b** (2.9 g, 10.1 mmol) as a white solid: mp = 96–97 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2995, 2931, 2870, 2850, 1594, 1571, 1458, 1430, 1325, 1209, 1149, 1058; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 6H), 1.63-1.70 (m, 4H), 2.59 (t, J = 6.2 Hz, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 25.0, 27.9, 35.7, 43.4), 55.5, 56.5, 94.1, 114.4, 120.5, 144.0, 154.0, 156.1. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{14}H_{19}ClO_2Na$ 277.0966, found: 277.0967.

6,8-Dimethoxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (S4a). To a stirred solution of tetralin **S2a** (1.6 g, 7.3 mmol) in acetonitrile (42 mL) was added cat. CuI (133 mg, 0.70 mmol) and 70% TBHP (8.8 mL) dropwise. The mixture was then allowed to react at 50 □ under N_2 for 6 h. After reaction was complete, reaction mixture was filtrated with celite and concentrated to give the crude oil. It was then redissolved with EtOAc (30 mL), washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was subjected to chromatography on silical gel with EtOAc/*n*-hexane (1:1) followed by EtOAc/*n*-hexane (2:1) to afford tetrlone **S4a** (906 mg, 53% yield) as a colorless oil: IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2962, 2938, 2866, 2840, 1671, 1595, 1571, 1454, 1324, 1246, 1215, 1158; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 6H), 1.92 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 6.35 (d, J = 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.6, 34.7, 36.2, 36.4, 55.1, 55.8, 96.1, 102.5, 115.1, 156.7, 162.1, 163.9, 196.3; HRMS (EI) m/z: [M] calcd. for $C_{14}H_{18}O_3$ 234.1256, found: 234.1253.

4-(Tert-butylperoxy)-5,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (S3a). Peroxide **S3a** (811 mg, 36%) was also isolated as a white solid: mp = 72–73 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2961, 2934, 2861, 2837, 1606, 1590, 1462, 1362, 1316, 1213, 1198, 1145; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (3H), 1.29 (s, 9H), 1.33 (s, 3H), 1.42 (dt, J = 13.2, 2.8 Hz, 1H), 1.62 (tt, J = 14.4, 2.8 Hz, 1H), 2.09 (td, J = 14.4, 2.8 Hz, 1H), 2.43 (dq, J = 13.2, 2.8 Hz, 1H), 3.81 (s, 6H), 5.24 (s, 1H), 6.30 (d, J =

2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.4, 26.7, 30.9, 31.4, 32.4, 34.4, 55.2, 55.2, 73.2, 79.7, 95.6, 102.7, 113.5, 150.7, 159.8, 160.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{18}H_{28}O_4Na$ 331.1880, found: 331.1877. To a stirred solution of peroxide **S3a** (811 mg, 2.60 mmol) in acetonitrile (26 mL) was added DBU (79 mg, 0.50 mmol).The mixture was then heated to reflux under N_2 for 48 h. After reaction was complete, the reaction solution was evaporated to give the crude oil, and was redissolved with EtOAc (30 mL), The organic layer was washed with 5% $HCl_{(aq)}$, water and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel to afford tetrlone **S4a** (493 mg, 81% yield) as a colorless oil.

4-(Tert-butylperoxy)-8-chloro-5,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (S3b). According to the synthetic procedures similar to compound **S3a**, peroxide **S3b** (789 mg, 23% yield) was prepared from tetralin **S2b** (2.6 g, 10.2 mmol) as a white solid: mp = 86–87 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2959, 2936, 2868, 1587, 1575, 1456, 1431, 1315, 1209, 1055; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (9H), 1.42 (s, 3H), 1.42-1.47 (m, 1H), 1.56 (tt, *J* = 13.2, 2.8 Hz, 1H), 1.61 (s, 3H), 2.19 (td, *J* = 14.4, 2.8 Hz, 1H), 2.38 (dq, *J* = 14.4, 2.8 Hz, 1H), 3.87 (s, 3H), 3.92 (s, 3H), 5.28 (s, 1H), 6.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0, 25.3, 26.7, 29.2, 35.9, 36.3, 55.6, 56.3, 73.5, 79.6, 94.4, 114.5, 115.8, 146.5, 156.6, 158.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{18}H_{27}ClO_4Na$ 365.1490, found: 365.1485.

5-Chloro-6,8-dimethoxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (S4b). According to the synthetic procedures similar to compound **S4a**, tetralone **S4b** (2.5 g, 91% combined yield) was prepared from tetralin **S2b** (2.6 g, 10.2 mmol) as a white solid: mp = 94–95 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2936, 2861, 1682, 1578, 1466, 1377, 1330, 1314, 1234, 1214, 1047; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (s, 6H), 1.97 (dd, *J* = 6.8, 4.8 Hz, 2H), 2.60 (dd, *J* = 6.8, 4.8 Hz, 2H), 3.91 (s, 3H), 3.96 (s, 3H), 6.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.7), 36.8, 36.8, 40.4, 56.3, 56.4, 95.0, 114.1, 117.3, 150.8, 159.6, 160.5, 196.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{14}H_{17}ClO_3Na$ 291.0758, found: 291.0760.

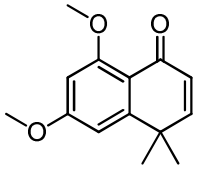
6,8-Bis(benzyloxy)-4,4-dimethylnaphthalen-1(4H)-one (9a). To a stirred solution of tetralone **S4a** (1.3 g, 5.6 mmol) in dry DCM (25 mL) was added BBr_3 (5.6 g, 22.5 mmol) at 0 □ under N_2. The mixture was then heated to reflux for 15 h. After reaction was complete, ice water was added to quench the reaction at 0 □, and then DCM was evaporated to give the crude residue, which was dissolved in EtOAc (50 mL) and filtrated with celite. The organic layer was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue. To the solution of crude residue in DMF (10 mL) was added Cs_2CO_3 (3.6 g, 11.1 mmol) and benzyl bromide (1.9 g, 11.1 mmol) at room temperature. The mixture was then stired

at 50 □ for 3 h under N_2. After reaction was complete, water was added to quench the reaction and the aqueous layer was extracted with EtOAc (50 mL). The organic extract was washed with water (20 mL x 3) and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:10) followed by EtOAc/*n*-hexane (1:2) to afford a mixture of compound **18a** and **9a** (1.1 g, ~ 2.8 mmol). To a solution of compound **18a** and **9a** in toluene (5 mL) was added DDQ (646 mg, 2.8 mmol) in one portion. The resulting mixture was then stirred at reflux temperature for 2 h. Saturated $NaHCO_{3(aq)}$ (5 mL) was added at room temperature to quench the reaction, and the aqueous layer was extracted with EtOAc (30 mL x 2). The organic extract was washed with saturated $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by chromatography on silical gel with EtOAc/*n*-hexane (1:10) followed by EtOAc/*n*-hexane (1:2) to afford enone **9a** (980 mg, 46% yield over 3 steps) as a white solid.

6,8-Bis(benzyloxy)-5-chloro-4,4-dimethylnaphthalen-1(4H)-one (9b). According to the synthetic procedures similar to compound **9a**, enone **9b** (838 mg, 40% yield over 3 steps) was prepared from tetralone **S4b** (1.3 g, 4.9 mmol) as a white solid.

Characterization of other new building blocks:

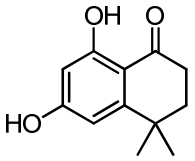
2-Chloro-3,5-dibenzloxy-α-methylstyrene (13b). Colorless oil; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3065, 3032, 2914, 2871, 1581, 1424, 1374, 1338, 1163, 1028; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.10 (s, 3H), 4.96 (s, 1H), 5.00 (s, 2H), 5.10 (s, 2H), 5.21 (s, 1H), 6.47 (d, J = 2.8 Hz, 1H), 6.56 (d, J = 2.8 Hz, 1H), 7.32-7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.2, 70.2, 70.7, 100.7, 107.2, 112.8, 115.7, 127.0, 127.5, 127.9, 128.0, 128.5, 128.5, 136.3, 136.4, 144.6, 154.8, 157.6; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{23}H_{22}ClO_2$ 365.1303, found: 365.1309.



S5

6,8-Dimethoxy-4,4-dimethylnaphthalen-1(4H)-one (S5).

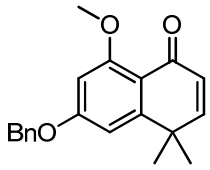
White solid; mp = 76–77 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 2966, 2935, 2878, 2842, 1659, 1633, 1596, 1573, 1455, 1324, 1258, 1220, 1138, 1036; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 6H), 3.90 (s, 3H), 3.93 (s, 3H), 6.22 (d, J = 10.4 Hz, 1H), 6.43 (s, 1H), 6.58 (s, 1H), 6.66 (d, J = 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5, 38.0, 55.3, 56.1, 96.8, 103.2, 114.4, 128.2, 152.8, 154.9, 162.5, 163.3, 184.1; HRMS (EI) m/z: [M] calcd. for $C_{14}H_{16}O_3$ 232.1099, found: 232.1093.



S6

6,8-Dihydroxy-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (S6).

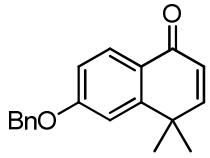
White solid; mp = 142–143 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3260 (br), 2964, 2868, 1626, 1602, 1448, 1358, 1232, 1157; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 6H), 1.93 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 5.71 (br s, 1H), 6.22 (d, J = 2.2 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 13.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.4, 34.1, 34.3, 36.3, 101.1, 105.1, 110.2, 156.5, 163.6, 165.9, 203.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{12}H_{14}O_3Na$ 229.0835, found: 229.0834.



S7

6-(Benzyloxy)-8-methoxy-4,4-dimethylnaphthalen-1(4H)-one (S7).

White solid; mp = 117–118 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3033, 2965, 2932, 1657, 1632, 1596, 1454, 1258, 1138, 1025; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 6H), 3.91 (s, 3H), 5.14 (s, 2H), 6.22 (d, J = 10.0 Hz, 1H), 6.50 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 10.0 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 7.36-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.3, 37.7, 55.9, 70.0, 97.5, 104.0, 114.4, 127.4, 128.0, 128.1, 128.5, 135.9, 152.7, 154.6, 162.3, 162.3, 183.8; HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{20}H_{20}O_3Na$ 331.1305, found: 331.1306.



S8

6-(benzyloxy)-4,4-dimethylnaphthalen-1(4H)-one (S8).

White solid; mp = 121–122 □; IR (CH_2Cl_2 cast, cm^{-1}) ν_{max} 3065, 3033, 2965, 2924, 2854, 1659, 1598, 1306, 1236, 1015; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 6H), 5.15 (s, 2H), 6.33 (d, J = 10.0 Hz, 1H), 6.85 (d, J = 10.0 Hz, 1H), 7.00 (dd, J = 8.8, 2.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.34-7.47 (m, 5H), 8.16 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.7, 37.6, 70.1, 112.1, 113.3, 124.3, 126.3, 127.5, 128.2, 128.6, 129.2, 136.1, 152.0, 156.7, 162.1, 184.2; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{19}H_{19}O_2$ 279.1380, found: 279.1381.

In Vitro Studies: MIC Determination. Minimum inhibitory concentration (MIC) of each compound was determined using broth microdilution method following the guidelines of the Clinical and Laboratory Standards Institute. Briefly, a 0.5 McFarland standard suspension of each test isolate was prepared using colonies from an overnight sheep blood agar plate and then diluted 1:100 in cation-adjusted Mueller-Hinton broth (CAMHB) to obtain an final inoculum of 1–1.5 x 10^6 CFU/mL. Fifty µl of the inoculum was then dispensed into wells containing 50 μL of test compound prepared in CAMHB containing 0.2% DMSO. The plates were then incubated at 35 ^{o}C ambient air overnight and read at 20 and 24 h after incubation.

ASSOCIATED CONTENT

Supporting Information

Scheme S1: the first-generation route for **9a** and **9b**; the ratio of *p*-quinone to hemiketal of **35**; spectral date of synthetic molecules **1**, **2** and **6** vs their natural counterparts; copies of ^{1}H and ^{13}C NMR spectra for all new compounds; bioactivity assay protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-Mail: cclin66@mx.nthu.edu.tw (C.-C. Lin)

*E-mail: ksshia@nhri.org.tw (K.-S. Shia)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Health Research Institutes and Ministry of Science and Technology of Taiwan (MOST 106-2113-M-400-004-MY2) for financial support.

REFERENCES

1. (a) Fischbach, M. A.; Walsh, C. T. Antibiotics for Emerging Pathogens. *Science* **2009,** *325*, 1089-1093. (b) Cooper, M. A.; Shlaes, D. Fix the Antibiotics Pipeline. *Nature* **2011,** *472*, 32. (c) Lewis, K. Antibiotics: Recover the Lost Art of Drug Discovery. *Nature* **2012,** *485*, 439-440.

2. (a) Chambers, H. F.; Deleo, F. R. Waves of Resistance: *Staphylococcus aureus* in the Antibiotic Era. *Nat. Rev. Microbiol.* **2009,** *7*, 629-641. (b) Boucher, H.; Miller, L.

G.; Razonable, R. R. Serious Infections Caused by Methicillin-Resistant *Staphylococcus aureus. Clin. Infect. Dis.* **2010,** *51*, S183-197.

3. (a) Marty, F. M.; Yeh, W. W.; Wennersten, C. B.; Venkataraman, L.; Albano, E.; Alyea, E. P.; Gold, H. S.; Baden, L. R.; Pillai, S. K. Emergence of a Clinical Daptomycin-Resistant *Staphylococcus aureus* Isolate During Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Osteomyelitis. *J. Clin. Microbiol.* **2006,** *44*, 595-597. (b) Howden, B. P.; Davies, J. K.; Johnson, P. D.; Stinear, T. P.; Grayson, M. L. Reduced Vancomycin Susceptibility in *Staphylococcus aureus*, Including Vancomycin-Intermediate and Heterogeneous Vancomycin-Intermediate Strains: Resistance Mechanisms, Laboratory Detection, and Clinical Implications. *Clin. Microbiol. Rev.* **2010,** *23*, 99-139. (c) Endimiani, A.; Blackford, M.; Dasenbrook, E. C.; Reed, M. D.; Bajaksouszian, S.; Hujer, A. M.; Rudin, S. D.; Hujer, K. M.; Perreten, V.; Rice, L. B.; Jacobs, M. R.; Konstan, M. W.; Bonomo, R. A. Emergence of Linezolid-Resistant *Staphylococcus aureus* After Prolonged Treatment of Cystic Fibrosis Patients in Cleveland, Ohio. *Antimicrob. Agents Chemother.* **2011,** *55*, 1684-1692. (d) Sun, Y.; Cai, Y.; Liu, X.; Bai, N.; Liang, B.; Wang, R. The Emergence of Clinical Resistance to Tigecycline. *Int. J. Antimicrob. Agents* **2013,** *41*, 110-116.

4. (a) Aoyagi, T.; Aoyama, T.; Kojima, F.; Matsuda, N.; Maruyama, M.; Hamada, M.; Takeuchi, T. Benastatins A and B, New Inhibitors of Glutathione S-Transferase, Produced by *Streptomyces sp.* MI384-DF12. I. Taxonomy, Production, Isolation, Physico-Chemical Properties and Biological Activities. *J. Antibiot.* **1992,** *45*, 1385-1390. (b) Aoyama, T.; Naganawa, H.; Muraoka, Y.; Nakamura, H.; Aoyagi, T.; Takeuchi, T.; Iitaka, Y. Benastatins A and B, New Inhibitors of Glutathione S-Transferase, Produced by *Streptomyces sp.* MI384-DF12. II. Structure Determination of Benastatins A and B. *J. Antibiot.* **1992,** *45*, 1391-1396. (c) Kodali, S.; Galgoci, A.; Young, K.; Painter, R.; Silver, L. L.; Herath, K. B.; Singh, S. B.; Cully, D.; Barrett, J. F.; Schmatz, D.; Wang, J. Determination of Selectivity and Efficacy of Fatty Acid Synthesis Inhibitors. *J. Biol. Chem.* **2005,** *280*, 1669-1677. (d) Feng, Z.; Kallifidas, D.; Brady, S. F. Functional Analysis of Environmental DNA-Derived Type II Polyketide Synthases Reveals Structurally Diverse Secondary Metabolites. *Proc. Natl. Acad. Sci. U.S.A.* **2011,** *108*, 12629-12634. (e) Kallifidas, D.; Kang, H. S.; Brady, S. F. Tetarimycin A, An MRSA-Active Antibiotic Identified Through Induced Expression of Environmental DNA Gene Clusters. *J. Am. Chem. Soc.* **2012,** *134*, 19552-19555. (f) Fukumoto, A.; Kim, Y. P.; Iwatsuki, M.; Hirose, T.; Sunazuka, T.; Hanaki, H.; Omura, S.; Shiomi, K. Naphthacemycins, Novel Circumventors of *β*-Lactam Resistance in MRSA, Produced by *Streptomyces sp.* KB-3346-5. II. Structure Elucidation. *J. Antibiot.* **2017,** *70*, 568-573. (g) Fukumoto, A.; Kim, Y. P.;

Matsumoto, A.; Takahashi, Y.; Suzuki, M.; Onodera, H.; Tomoda, H.; Matsui, H.; Hanaki, H.; Iwatsuki, M.; Omura, S.; Shiomi, K. Naphthacemycins, Novel Circumventors of *β*-Lactam Resistance in MRSA, Produced by *Streptomyces sp.* KB-3346-5. I. The Taxonomy of the Producing Strain, and the Fermentation, Isolation and Antibacterial Activities. *J. Antibiot.* **2017,** *70*, 562-567. (h) Qin, Z.; Munnoch, J. T.; Devine, R.; Holmes, N. A.; Seipke, R. F.; Wilkinson, K. A.; Wilkinson, B.; Hutchings, M. I. Formicamycins, Antibacterial Polyketides Produced by *Streptomyces formicae* Isolated from African *Tetraponera* Plant-Ants. *Chem. Sci.* **2017,** *8*, 3218-3227.

5. Feng, Z.; Chakraborty, D.; Dewell, S. B.; Reddy, B. V.; Brady, S. F. Environmental DNA-Encoded Antibiotics Fasamycins A and B Inhibit FabF in Type II Fatty Acid Biosynthesis. *J. Am. Chem. Soc.* **2012,** *134*, 2981-2987.

6. (a) Huang, J.-K.; Yang Lauderdale, T.-L.; Shia, K.-S. Studies on Antibiotics Active against Resistant Bacteria. Total Synthesis of MRSA-Active Tetarimycin A and Its Analogues. *Org. Lett.* **2015,** *17*, 4248-4251. (b) Hirose, T.; Kojima, Y.; Matsui, H.; Hanaki, H.; Iwatsuki, M.; Shiomi, K.; Omura, S.; Sunazuka, T. Total Synthesis of (±)-Naphthacemycin A_9, Possessing Both Antibacterial Activity Against Methicillin-Resistant *Staphylococcus aureus* and Circumventing Effect of *β*-Lactam Resistance. *J. Antibiot.* **2017,** *70*, 574-581.

7. (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The Economies of Synthesis. *Chem. Soc. Rev.* **2009,** *38*, 3010-3021. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox Economy in Organic Synthesis. *Angew. Chem. Int. Ed.* **2009,** *48*, 2854-2867.

8. (a) Mitchell, A. S.; Russell, R. A. Annulation Reactions with Stabilized Phthalide Anions. *Tetrahedron* **1995,** *51*, 5207-5236. (b) Rathwell, K.; Brimble, M. A. Use of Stabilized Phthalide Anion Annulation Reactions in Synthesis: An Update. *Synthesis* **2007,** *2007*, 643-662. (c) Mal, D.; Pahari, P. Recent Advances in the Hauser Annulation. *Chem. Rev.* **2007,** *107*, 1892-1918. (d) Donner, C. D. Tandem Michael–Dieckmann/Claisen Reaction of *Ortho*-Toluates—the Staunton–Weinreb Annulation. *Tetrahedron* **2013,** *19*, 3747-3773.

9. (a) Koch, K.; Podlech, J.; Pfeiffer, E.; Metzler, M. Total Synthesis of Alternariol. *J. Org. Chem.* **2005,** *70*, 3275-3276. (b) Donohoe, T. J.; Jones, C. R.; Barbosa, L. C. Total synthesis of (±)-Streptonigrin: De Novo Construction of a Pentasubstituted Pyridine Using Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2011,** *133*, 16418-16421. (c) Noble, A.; Roesner, S.; Aggarwal, V. K. Short Enantioselective Total Synthesis of Tatanan A and 3-epi-Tatanan A Using Assembly-Line Synthesis. *Angew. Chem. Int. Ed.* **2016,** *55*, 15920-15924.

10. (a) Lo, J. C.; Yabe, Y.; Baran, P. S. A Practical and Catalytic Reductive Olefin Coupling. *J. Am. Chem. Soc.* **2014,** *136*, 1304-1307. (b) Lo, J. C.; Kim, D.; Pan, C. M.;

Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. Fe-Catalyzed C-C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017,** *139*, 2484-2503.

11. (a) Chin, C.-L.; Tran, D. D.-P.; Shia, K.-S.; Liu, H.-J. The Total Synthesis of Pygmaeocin C. *Synlett* **2005,** *2005*, 417-420. (b) Baumann, T.; Vogt, H.; Bräse, S. The Proline-Catalyzed Asymmetric Amination of Branched Aldehydes. *Eur. J. Org. Chem.* **2007,** *2007*, 266-282.

12. (a) Lafleur-Lambert, R.; Boukouvalas, J. Asymmetric Total Synthesis of (+)-*o*-Methylasparvenone, a Rare Nitrogen-Free Serotonin 2C Receptor Antagonist. *Org. Biomol. Chem.* **2016,** *14*, 8758-8763. (b) Guo, Y. A.; Zhao, M.; Xu, Z.; Ye, T. Total Synthesis and Stereochemical Assignment of Actinoranone. *Chem. Eur. J.* **2017,** *23*, 3572-3576.

13. Zhao, G.; Xu, G.; Qian, C.; Tang, W. Efficient Enantioselective Syntheses of (+)-Dalesconol A and B. *J. Am. Chem. Soc.* **2017,** *139*, 3360-3363.

14. (a) Makara, G. M.; Anderson, W. K. An Efficient Synthesis of 5,7-Dimethoxy-4-methylphthalide, a Key Intermediate in the Synthesis of Mycophenolic Acid. *J. Org. Chem.* **1995,** *60*, 5717-5718. (b) Garbaccio, R. M.; Danishefsky, S. J. Efficient Asymmetric Synthesis of Radicicol Dimethyl Ether: A Novel Application of Ring-Forming Olefin Metathesis. *Org. Lett.* **2000,** *2*, 3127-3129.

15. (a) Tanaka, M.; Ohshima, T.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. Total Syntheses of the Lignans Isolated from Schisandra Chinensis. *Tetrahedron* **1995,** *51*, 11693-11702. (b) Koci, J.; Grandclaude, V.; Massonneau, M.; Richard, J. A.; Romieu, A.; Renard, P. Y. A Novel and Unusually Long-Lived Chemiluminophore Based on the 7-Hydroxycoumarin Scaffold. *ChemComm* **2011,** *47*, 6713-6715.

16. (a) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995,** *95*, 2457-2483. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005,** *127*, 4685-4696.

17. (a) Anzini, M.; Cappelli, A.; Vomero, S.; Seeber, M.; Menziani, M. C.; Langer, T.; Hagen, B.; Manzoni, C.; Bourguignon, J. J. Mapping and Fitting the Peripheral Benzodiazepine Receptor Binding Site by Carboxamide Derivatives. Comparison of Different Approaches to Quantitative Ligand-Receptor Interaction Modeling. *J. Med. Chem.* **2001,** *44*, 1134-1150. (b) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. Nucleophilic Addition to 3-Substituted Pyridinium Salts: Expedient Syntheses of (-)-L-733,061 and (-)-CP-99,994. *Org. Lett.* **2004,** *6*, 3517-3520. (c) Kobayashi, S.; Inoue, T.; Ando, A.; Tamanoi, H.; Ryu, I.; Masuyama, A. Total Synthesis and Structural Revision of Hericerin. *J. Org. Chem.* **2012,** *77*, 5819-5822.

18. (a) Okazaki, K.; Nomura, K.; Yoshii, E. An Efficient Synthesis of 3-Cyano-1(3H)-isobehzofuranones. *Synth. Commun.* **1987,** *17*, 1021-1027. (b) Magauer, T.; Smaltz, D. J.; Myers, A. G. Component-Based Syntheses of Trioxacarcin A, DC-45-A1 and Structural Analogues. *Nat. Chem.* **2013,** *5*, 886-893. (c) Karmakar, R.; Mal, D. Total Synthesis of Chlorocyclinone A, a PPAR-γ Antagonist. *J. Org. Chem.* **2012,** *77*, 10235-10248. (d) Brimble, M. A.; Hassan, N. P.; Naysmith, B. J.; Sperry, J. Toward an Asymmetric Synthesis of the Dimeric Pyranonaphthoquinone Antibiotic Crisamicin A. *J. Org. Chem.* **2014,** *79*, 7169-7178. (e) Nicolaou, K. C.; Wang, Y.; Lu, M.; Mandal, D.; Pattanayak, M. R.; Yu, R.; Shah, A. A.; Chen, J. S.; Zhang, H.; Crawford, J. J.; Pasunoori, L.; Poudel, Y. B.; Chowdari, N. S.; Pan, C.; Nazeer, A.; Gangwar, S.; Vite, G.; Pitsinos, E. N. Streamlined Total Synthesis of Uncialamycin and Its Application to the Synthesis of Designed Analogues for Biological Investigations. *J. Am. Chem. Soc.* **2016,** *138*, 8235-8246.

19. (a) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. Regiospecific One-Step Annelations via Quinone Monoacetals. *J. Chem. Soc., Chem. Commun.* **1980**, 932-933. (b) Roy, H. N.; Rahman, A. F. M. M.; Islam, M. A. Regiospecific Synthesis of Carboxylated and Simple α-Tetralones with Homophthalates and Various Acrylates by a Simple Condensation Method. *J. Chem. Res.* **2003,** 594-596. (c) Nicolaou, K. C.; Hale, C. R.; Nilewski, C.; Ioannidou, H. A.; ElMarrouni, A.; Nilewski, L. G.; Beabout, K.; Wang, T. T.; Shamoo, Y. Total Synthesis of Viridicatumtoxin B and Analogues Thereof: Strategy Evolution, Structural Revision, and Biological Evaluation. *J. Am. Chem. Soc.* **2014,** *136*, 12137-12160.

20. Bauta, W. E.; Lovett, D. P.; Cantrell, W. R., Jr.; Burke, B. D. Formal Synthesis of Angiogenesis Inhibitor NM-3. *J. Org. Chem.* **2003,** *68*, 5967-5973.

21. Mali, R. S.; Jagtap, P. G.; Tilve, S. G. Convenient Synthesis of Naturally Occurring Methoxy-and Hydroxy Phthalides. *Synth. Commun.* **1990,** *20*, 2641-2652.

22. Adachi, S.; Watanabe, K.; Iwata, Y.; Kameda, S.; Miyaoka, Y.; Onozuka, M.; Mitsui, R.; Saikawa, Y.; Nakata, M. Total Syntheses of Lactonamycin and Lactonamycin Z with Late-Stage A-Ring Formation and Glycosylation. *Angew. Chem. Int. Ed.* **2013,** *52*, 2087-2091.

23. Podlesny, E. E.; Carroll, P. J.; Kozlowski, M. C. Selective Oxidation of 8,8'-Hydroxylated Binaphthols to Bis-spironaphthalenones or Binaphtho-*para*- and Binaphtho-*ortho*-quinones. *Org. Lett.* **2012,** *14*, 4862-4865.

24. Lubbe, M.; Langer, P. Synthesis of 3-Hydroxy-5-alkoxyhomophthalates by Domino '2 : 1-Coupling/Intramolecular Aldol Condensation' Reactions of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Tetraalkoxymethanes. *Org. Biomol. Chem.* **2010,** *8*, 881-885.

25. Parlow, J. J. Syntheses of Tetrahydronaphthalenes. Part II. *Tetrahedron* **1994,** *50*,

3297-3314.