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Synthesis of Antifungal Glucan Synthase Inhibitors from Enfumafungin

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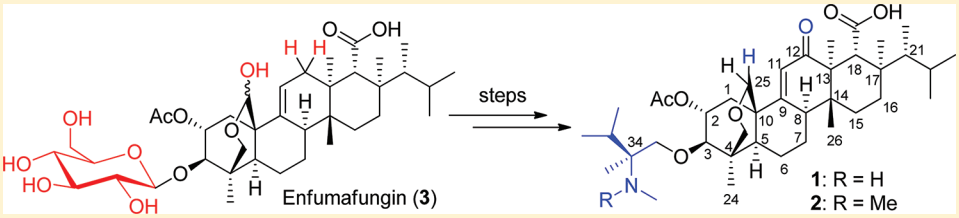
Supporting Information



ABSTRACT: An efficient, new, and scalable semisynthesis of glucan synthase inhibitors **1** and **2** from the fermentation product enfumafungin **3** is described. The highlights of the synthesis include a high-yielding ether bond-forming reaction between a bulky sulfamidate **17** and alcohol **4** and a remarkably chemoselective, improved palladium(II)-mediated Corey-Yu allylic oxidation at the highly congested C-12 position of the enfumafungin core. Multi-hundred gram quantities of the target drug candidates **1** and **2** were prepared, in 12 linear steps with 25% isolated yield and 13 linear steps with 22% isolated yield, respectively.

INTRODUCTION

The incidence of systemic fungal infections has risen dramatically over recent decades due to the increasing number of immunocompromised patients as well as the expanded use of invasive medical procedures and broad spectrum antibiotics.[1] The major antifungal therapeutic reagents for the treatment of systemic fungal infections, including the polyenes, azoles, and echinocandins, are often limited by their side effects, clinical resistance, and a narrow spectrum of antifungal activity.[2] Enfumafungin **3**[3] isolated from a fermentation of *Hormonema* sp. is capable of inhibiting fungal glucan synthase. As part of an ongoing drug discovery program at Merck Research Laboratories, two novel enfumafungin derivatives, **1** and **2**, were identified as potent glucan synthase inhibitors[4] and selected for further development.

Early syntheses[5] of **1** and **2** involved 15 and 13 steps in the longest linear sequence, respectively, with approximately 11% and 17% yields. Besides the low overall yields, the original procedures were not suitable for scale-up due to the use of certain impractical and hazardous processes (*vide infra*). In order to support further study of the pharmacological properties of **1** and **2**, efficient and reliable syntheses were required. We report herein practical and scaleable syntheses of **1** and **2**, including a detailed account of the issues presented by these challenging substrates.

RESULTS AND DISCUSSION

Initial Medicinal Chemistry Route. The original medicinal chemistry route starting from **3** is summarized in Scheme 1. In comparing our targets **1** and **2** with enfumafungin, it appears that the following three chemical modifications are required: (1) reduction of the lactol group at position C-25; (2) removal of the glucose and installation of the appropriate side chains at C-3; and (3) allylic oxidation at C-12. Previous work[5] at Merck Research Laboratories and Scynexis Inc. indicated that the allylic oxidation would only proceed reasonably well on a substrate bearing an amide group at C-18. The overall synthetic schemes for **1** and **2** looked amenable to scale-up, but we identified a few potentially demanding steps. First of all, the use of 2.5 equiv of KH (see **4** → **6**, Scheme 1) was not advisible for any large scale reaction. Second, while Birch-type or other similar reductions (e.g., **6** → **7**, Scheme 1) can be applied on large scale, our preference was to avoid this transformation due to the hazards represented by the handling of highly activated elemental alkali metals and the requirement of special apparatus.[6] Third and most importantly, the allylic oxidation required 45 equiv of CrO_3 and 3,5-dimethylpyrazole in 380 volumes of CH_2Cl_2. The use of such a large excess of highly toxic CrO_3 and large volumes of a chlorinated solvent are not in accordance green chemistry principles. In addition, we also had difficulty removing residual chromium to acceptable levels in the final products **1** and **2**. Furthermore, the resulting enone was found to be unstable in the crude reaction mixture, requiring immediate silica gel column chromatography purification to secure the oxidized product and leading to unacceptably low yields upon scaling up to 10 g.

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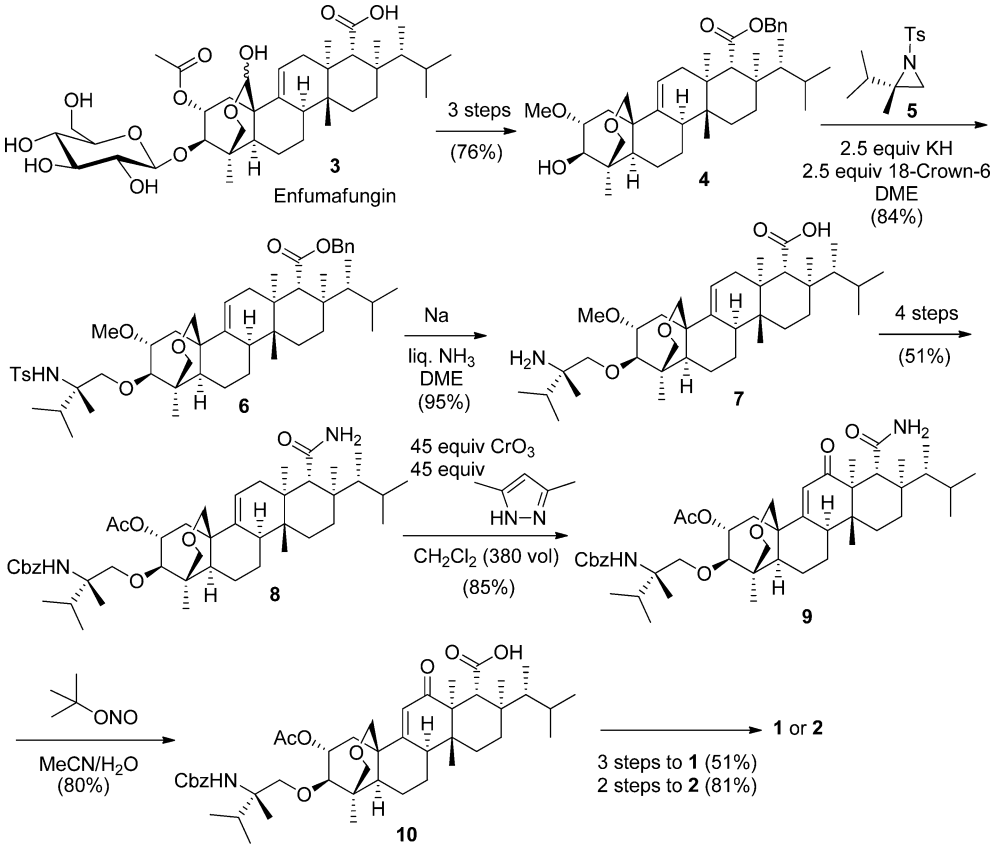
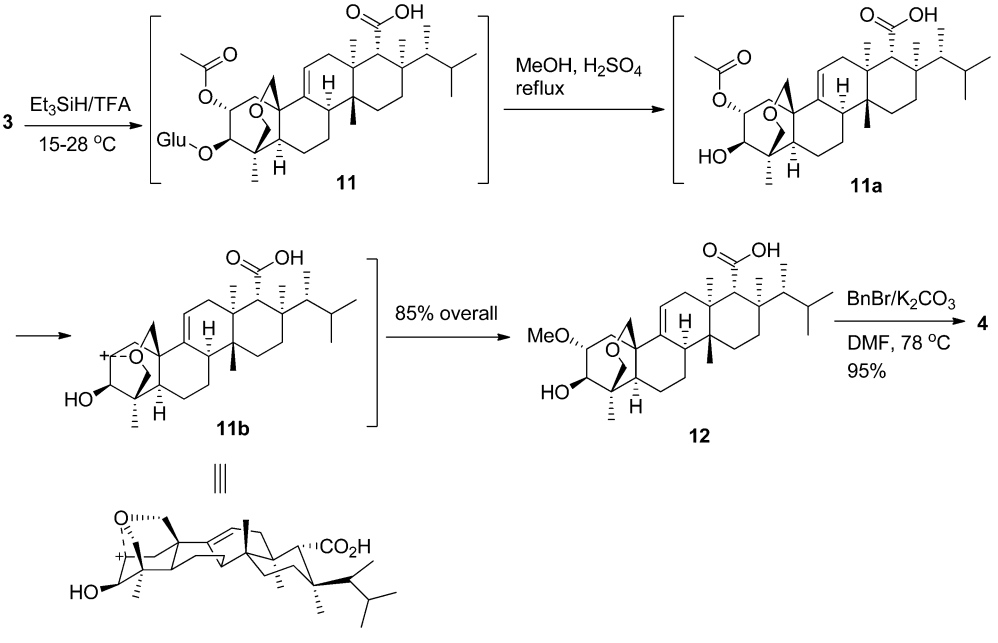
Scheme 1. Medicinal Chemistry Route for 1 and 2



Scheme 2



In addition to the challenging synthetic problems presented by targets **1** and **2**, the issue of final crystalline form for the active pharmaceutical ingredient (API) was not resolved at the outset of our studies. Early isolations of **1** and **2** were via lyophilization (amorphous solids), and so development of a reproducible crystallization was also required.

Preparation of Benzyl Ester 4. The first three steps of the synthesis of the benzyl ester **4** from enfumafungin **3** were optimized as shown in Scheme 2. Hydroxyl acid **12** was obtained from **3** by reduction of the lactol using Et_3SiH and TFA in toluene, followed by deglycosylation in methanol in the presence of sulfuric acid. Crystalline **12** was isolated by direct crystallization from MeOH/water (1:1) in 85% yield. It is

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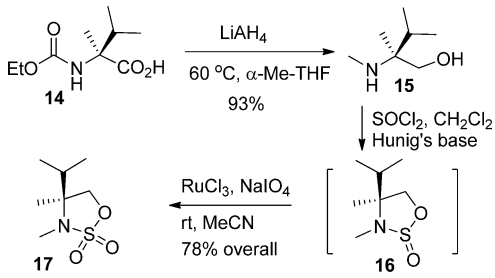
worth noting that **12** needed to be washed with 5% NaOAc(aq)/water (1:1) to ensure neutral pH prior to drying, otherwise decomposition catalyzed by the remaining sulfuric acid occurred.[7] Facial selection of the methoxy group at C-2 position was perfectly controlled likely by neighboring participation of the oxygen of the cyclic ether (**11b**). The methyl ester of the carboxylic acid **12** is not formed under refluxing $MeOH/H_2SO_4$ likely due to steric congestion that inhibits nucleophilic attack at the carbonyl.[8] In contrast, selective benzylation of the carboxylic acid group in **12** was accomplished with benzyl bromide and K_2CO_3 in DMF. The reaction with K_2CO_3 was cleaner than the original reaction conditions with $NaHCO_3$, and isolated yield of crystalline compound **12** was improved from 88% to 95% yield.

Installation of the Side Chain. Originally, installation of the side chain of compounds **1** and **2** was achieved by S_N2 opening of an *N*-tosylated aziridine with *in situ* preparation of the potassium alkoxide of **4** using KH and 18-crown-6.[5] However, subsequent removal of the *N*-tosyl protecting group required the undesirable Birch reduction conditions alluded to previously. Cyclic sulfamidates are known to be versatile intermediates for the synthesis of various heteroatomic functional compounds.[9] We envisaged that the ether bond of compounds **1** and **2** could be accessed through a ring opening of a five-membered cyclic sulfamidate.

Since both **1** and **2** have a methyl group on the nitrogen atom, *N*-methyl cyclic sulfamidate **17** was designed to circumvent this problem. Sulfamidate **17** was prepared from *N*-protected amino acid **14**[10] in three steps as shown in Scheme 3. Treatment of compound **14** with LAH afforded *N*-methyl amino alcohol **15** in 93% yield, which was converted to sulfamidite **16** by treatment with thionyl chloride in the presence of Hünig's base. Direct oxidation of crude sulfamidite **16** with $NaIO_4$ in the presence of catalytic amount of $RuCl_3$ afforded desired crystalline sulfamidate **17** in 78% overall yield. Upon crystallization of **17**, a little upgrade of ee was observed.

Scheme 3



With both alcohol **4** and sulfamidate **17** in hand, preliminary investigation confirmed that the S_N2 reaction coupling these two fragments did proceed in the presence of KH and 18-crown-6. Amine **19** was isolated in >90% yield via sulfamide **18** after adjustment of pH. However, the use of large amount of pyrophoric KH is not recommended from a safety point of view, so alternative bases were screened for the S_N2 displacement reaction, including NaH, KHMDS, KO^{t}Bu, and potassium *tert*-pentoxide in place of potassium hydride. As shown in Table 1, using NaH as base in DME or DMAc in the presence of 15-crown-5 ether afforded 50% and 70% conversion, respectively (entries 2 and 3). The coupling reaction using KHMDS as base gave high conversion but provided *O*-TMS silylated compound **4** as the major product (entry 4). Encouraging results were obtained when the reaction was carried out with potassium *tert*-butoxide to give 80% conversion (entry 5). Azeotropic removal of *t*BuOH from the mixture of **4** and KO*t*Bu to force the complete generation of the potassium alkoxide of **4** failed even with extensive efforts. The result indicated poor equilibrium toward the potassium alkoxide in the reaction mixture. Fortunately, the coupling reaction proceeded to almost quantitative yield when more basic potassium *tert*-pentoxide (*t*-amylOK) was used instead of KO*t*Bu (entries 6–8). Also, the reaction worked well even without 18-crown-6 (entry 8).

Table 1. Optimization for the Alkoxide-Mediated Sulfamidate Opening

entry[a]	base (equiv)	solvent	crown ether[b]	*T* (°C)	*t* (h)	conv (%)[c]	yield (%)[d]
1	KH (2.0)	DME	18-C-6	rt	3	100	100
2	NaH (2.0)	DME	15-C-5	rt	12	50	
3	NaH (2.0)	DMAc	15-C-5	60	24	70	
4	KHMDS (1.2)	DME	18-C-6	rt	12	>90	<10[e]
5	*t*-BuOK (1.2)	THF/ DME	18-C-6	rt	12	80	
6	*t*-amylOK (1.2)	DME	18-C-6	rt	4	95	
7	*t*-amylOK (1.2)	DMAc	18-C-6	rt	2	>99	>99
8	*t*-amylOK (1.2)	DMAc	N/A	rt	24	>99	>99

[a]1.2 equiv of sulfamidate was used. [b]1 equiv of crown ether was used. [c]Measured by HPLC. [d]The assay yields were measured by HPLC against a quantitative standard. [e]TMS silylation of alcohol **6** was the major reaction.

Thus, after extensive optimization, amine **19** was obtained by treatment of alcohol **4** and 1.2 equiv of sulfamidate **17** in the presence of 1.2 equiv of potassium *tert*-pentoxide, followed by HCl–NaOH aqueous workup. Crude amine **19** was then heated with acetic acid in the presence of 2.49 equiv of *p*-toluenesulfonic acid monohydrate and acetic anhydride, followed by crystallization from acetonitrile/water (4:1) to afford colorless crystalline acetate **20** in 90% overall isolated yield from alcohol **4** (Scheme 4). Once again, the stereochemistry of C-2 position was completely controlled by the neighboring participation of the oxygen of the cyclic ether as previously mentioned.

Allylic Oxidation. The remaining chemical steps from **20** to target **1** were allylic oxidation and deprotection of the benzyl ester. In order to shorten the reaction sequence, allylic oxidations were screened from earlier intermediates, such as **20**, *N*-Cbz **21**, and *N*-Cbz carboxylic acid **22** (shown in Figure 1). Unfortunately, almost all allylic oxidations did not proceed well under many reported conditions.[11]

Among **20**, **13**, and **22**, allylic oxidation of **21** was rather promising, and results are summarized in Table 2. Substrate **21** was prepared in 95% yield by treatment of the free amine **20** with Cbz-chloride under Schotten-Bauman conditions. Initial attempts to oxidize **21** using CrO_3 in the presence of 3,5-dimethyl pyrazole in dichloromethane at ambient temperature resulted in 60% conversion. However, the HPLC assay of desired enone **23** was less than 5% yield (entry 1). The assay yields were improved a little up to 12% (entry 2) and 22% (entry 12) by Doyle's $[Rh_2(CAP)_4$ and TBHP$]$[11g,h,p] and Corey-Yu's [Pd/C or $Pd(OH)_2$ /C and TBHP][11n,o] allylic oxidation conditions, respectively. However, these improve-

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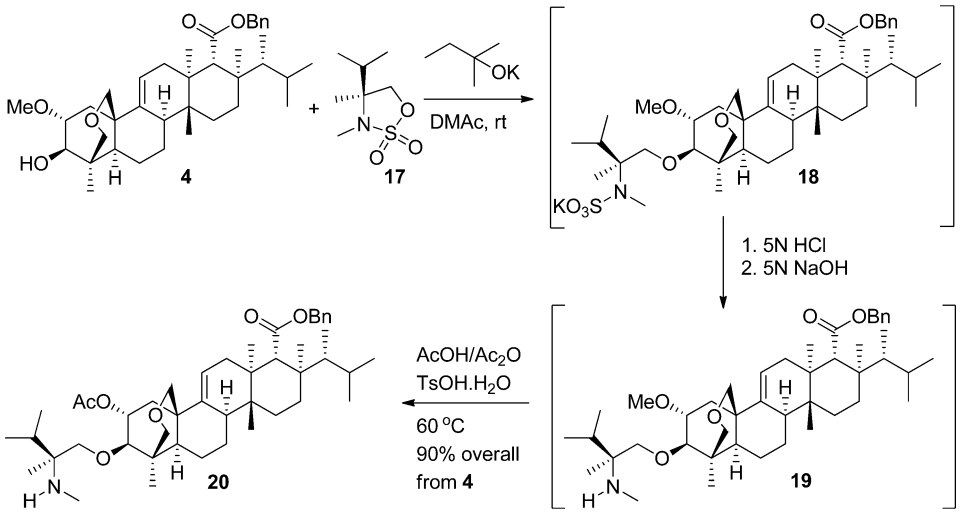
Scheme 4



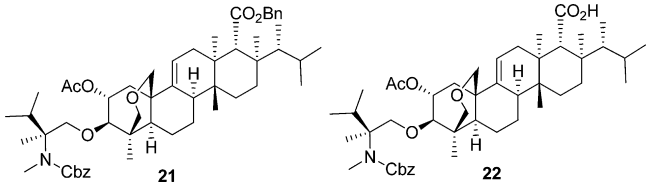


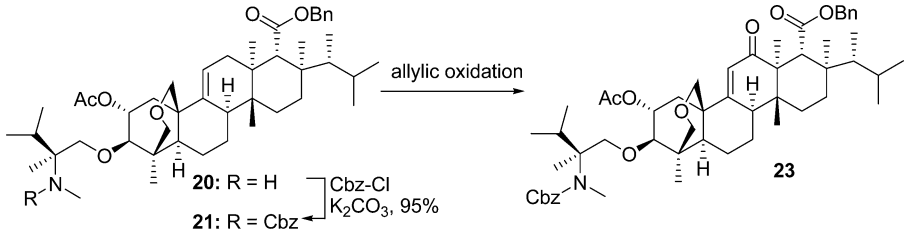
Figure 1. Substrates **21** and **22** for allylic oxidation.

ments of yield were not sufficient to run this oxidation on a larger scale, especially since we had only a very limited supply of expensive fermentation product starting material enfumafungin.

Subsequent controlled experimental studies showed that product **23** was unstable under the reaction conditions with or without oxidants. The double bond migration of **23** to the tetrasubstituted unconjugated position, followed by further oxidation, resulted in decomposition.

In a model study on the enfumafungin core skeleton without the side chain,[12] it was found that the allylic oxidation proceeded rather smoothly when the carboxylic acid at C-18 was converted to the corresponding carbamide, and the desired enone product was isolated in 40% yield under Doyle's conditions. Thus, it was decided allylic oxidation would be performed on the *N*-Cbz-protected corresponding carbamide **8**. Removal of benzyl group from **20** via transfer hydrogenation with a mixture of formic acid and triethylamine in the presence of Pd/C gave amino acid **24** in 98% HPLC yield against to a quantitative standard (Scheme 5). Without isolation of **24**, protection of the amine at the side chain was accomplished by Cbz chloride. Because the carboxylic acid reacted with Cbz chloride to form a stable mix-anhydride under Schotten-Bauman conditions, 2.5 equiv of Cbz-chloride was required to

Table 2. Optimization for the Allylic Oxidation of Benzyl Ester 21



entry	catalyst	additive	oxidant	solvent	*T* (°C)	*t* (h)	conv (%)	**23** (%)
1		3,5-DMP	CrO_3	CH_2Cl_2	rt	48	60	<5[a]
2	$Rh_2(CAP)_4$	K_2CO_3	TBHP	CH_2Cl_2	rt	42	70	12[a]
3	$Rh_2(CAP)_4$	K_2CO_3	TBHP	MeCN	rt	42	40	<5[a]
4	Pd/C	K_2CO_3	TBHP	MeCN	30	21	41	12[a]
5	$Pd(OTf)_2$	pyridine	TBHP	CH_2Cl_2	rt	48	10	0
6	$Pd(OH)_2/C$	K_2CO_3	TBHP	CH_2Cl_2	30	60	50	10[b]
7	$Pd(OH)_2/C$	K_2CO_3	TBHP	MeCN	30	21	44	13[a]
8	$Pd(OH)_2/C$	K_2CO_3	TBHP	EtOAc	30	24	61	15[a]
9	$Pd(OH)_2/C$	K_2CO_3	TBHP	EtOAc	5	62	64	17[a]
10	$Pd(OH)_2/C$	K_2CO_3	TBHP	*n*-C_3H_7CN	5	62	50	15[a]
11	$Pd(OH)_2/C$	Cs_2CO_3	TBHP	*n*-C_3H_7CN	−5	384	92	13[a]
12	$Pd(OH)_2/C$	K_2CO_3	TBHP	*n*-C_3H_7CN	−30	288	58	17[b] (22)[a]

[a]Assay yield by HPLC against a quantitative standard. [b]Isolated yield.

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Scheme 5

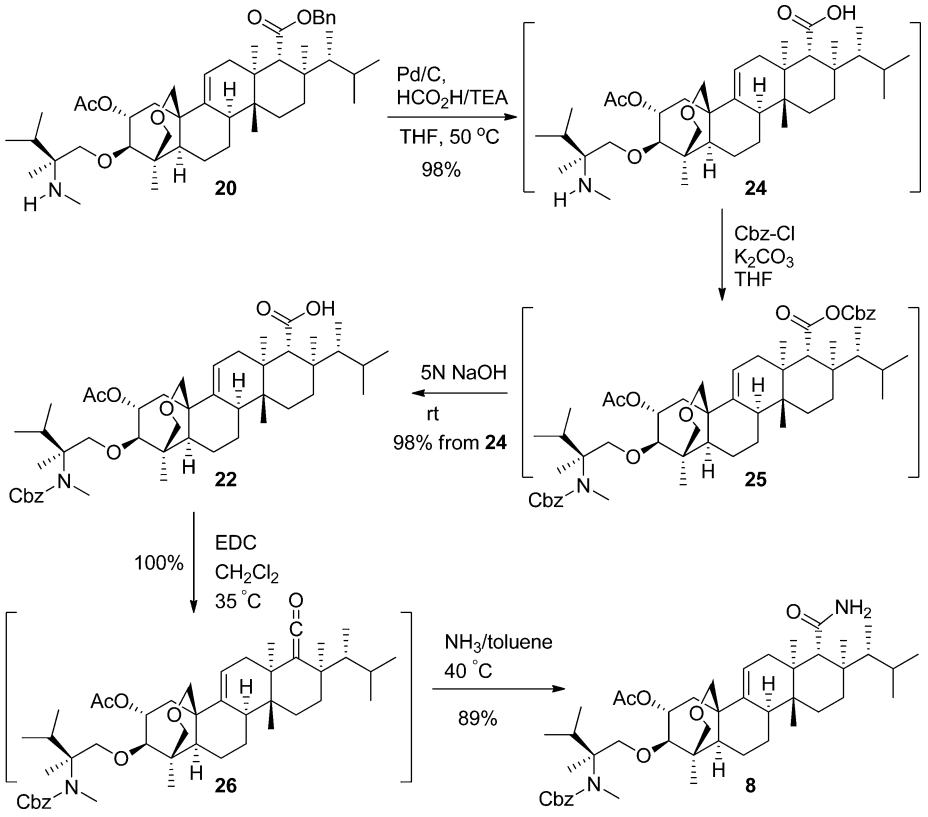
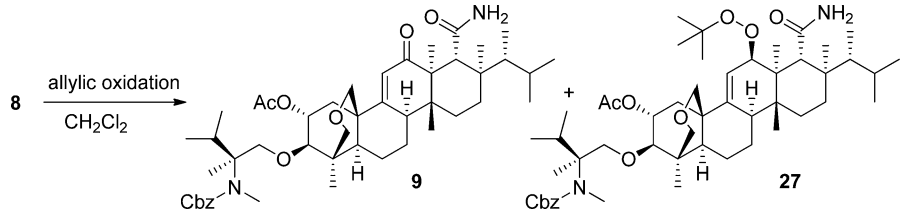


Table 3. Optimization of the Allylic Oxidation of Amide 8



entry	catalyst	additive	oxidant	T (°C)	t (h)	conv (%)	**9**:**27**	**9** (%)[b]
1		3,5-DMP[a]	CrO_3	−25 to 15	21	100		36
2	$Rh_2(CAP)_4$	K_2CO_3	TBHP	rt	70	>97	1.3:1	30
3	$Pd(OH)_2/C$	K_2CO_3	TBHP	rt	31	>97	1.3:1	34

[a]3,5-Dimethylpyrazole. [b]Assay yield by HPLC against a quantitative standard.

ensure the completion of *N*-Cbz protection. Selective hydrolysis of the resulting mixture anhydride **25** required unusually harsh conditions, heating with aqueous sodium hydroxide, and provided *N*-Cbz carboxylic acid **22** in high assay yield after removal of benzyl alcohol by a DMSO/water wash. Isolated acid **22** was converted to the corresponding stable ketene **26** by heating at 35 °C with EDC, and reaction of ketene **26** with ammonia at 40 °C gave the desired amide in 89% yield.[13]

With amide **8** in hand, we initiated our detailed studies on its allylic oxidation (Table 3). As mentioned previously, the initial medicinal chemistry conditions for this step involved 45 equiv of CrO_3 and 45 equiv of 3,5-dimethylpyrazole in 380 vol of CH_2Cl_2. By reducing the quantity of reagents and solvent [CrO_3 (15 equiv) and 3,5-dimethylpyrazole (15 equiv) in 50 vol of CH_2Cl_2], the isolated yield of the desired enone **9** decreased to 36% (Table 3, entry 1). Further decreasing the excess of reagents and solvent (5 equiv and 15 vol] resulted in low conversion and low assay yield of **9**. $Rh_2(CAP)_4$-mediated allylic oxidation of compound **8** by TBHP afforded a mixture of enone **9** and allylic *tert*-butylperoxy ether **27** in 1.3:1 ratio (entry 2) with an isolated yield of enone **9** of 30% after chromatographic purification. A similar result was observed with the allylic oxidation mediated by $Pd(OH)_2/C$ (entry 3). The stereochemistry of peroxide **27** was confirmed by NOE experiments as being β. As shown in Figure 2, when the protons of the *tert*-butyl group of **27** were irradiated, besides the olefin proton and C-12 proton, NOE enhancements to the proton of C-18 (0.5%), the C-26 methyl (0.5%), and the α-proton of C-25 (0.9%) were observed.

It is well documented that allylic *tert*-butylperoxy ethers such as **27** are readily converted to the corresponding enone under typical reaction conditions.[14] In practice, we did not observe any corresponding α-peroxide ether, which was apparently

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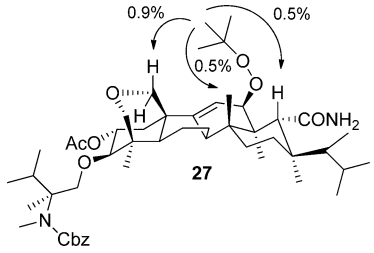

Figure 2. NOE Studies for **27**.

instantly converted to enone **9**. In contrast, the β-peroxide ether **27** was remarkably stable under the reaction conditions. Conversion of **27** to **9** was attempted under numerous conditions including treatment of **20** with base (e.g., TEA, DBU, K_2CO_3), transition metals (e.g., CuCl, $CuCl_2$, $NiCl_2$, $CoCl_2$, $FeCl_3$, Pd/C with or without TBHP), and UV lamp at low or high temperature. All conditions resulted in no reaction or decomposition.

The surprising inertness of this β-peroxide directed our attention to the stereochemical aspects of this system. As reported by Corey and Yu,[11n,o] the allylic oxidation proceeds by a radical mechanism and allylic radical **28** would be the expected intermediate for this reaction (Figure 3). Considering the stereochemical environment of radical **28**, it was not surprising that a nucleophilic ($^tBuO_2M$) would more readily approach the molecule from the α-face than from the β-face due to a 1,3-diaxial interaction with the C-26 methyl groups. Peroxide attack from the α-face produced an unobserved hypothetical peroxide intermediate **29**, which spontaneously collapses to enone **9** with abstraction of a C-12 axial proton either by base or by the *tert*-butylperoxy radical. On the other hand, a nucleophilic attack from the β-face generates the stable *tert*-butylperoxy ether **27**, in which the C-12 equatorial proton cannot readily be abstracted, either by a base or by a *tert*-butylperoxy radical under the allylic oxidation conditions. The reason why this abstraction is so kinetically disfavored is not clear. It might be worth noting that the C ring of **27** would be expected to adopt a twisted boat conformation in which the C-12 equatorial proton would be forced to move into a sterically congested pocket.

Since the β-face of the radical intermediate **28** is more hindered than the α-face, the ratio of enone **9** and peroxide **27** would be improved if a bulkier oxidant, such as cumene hydroperoxide (CHP) instead of *tert*-butylhydroperoxide, was employed. Indeed, with CHP as oxidant the ratio of desired product **9** to peroxides (**27** + **30**) improved to ~7:1 while HPLC assay yield increased to 64% from 34%.[15]

Completion of the Synthesis. With enone **9** in hand, the primary amide was converted to the acid **10** by treatment with *tert*-butyl nitrite in aqueous acetonitrile in 83% isolated yield after crystallization. Finally, cleavage of the *N*-Cbz-protected group by hydrogenation in the presence of $Pd(OH)_2/C$ and acetic acid afforded drug candidate **1** in 98% yield after crystallization from ethyl acetate and methanol. Reductive *N*-methylation of **1** with formaldehyde in the presence of sodium cyanoborohydride furnished the synthesis of the second drug candidate **2** in 90% yield after crystallization from isopropanol, as summarized in Scheme 6.

Treatment of compound **1** with sodium bicarbonate, following by hydrogen chloride in isopropanol afforded crystalline compound **31** in 86% overall yield. Single crystals of compound **31** as an acetonitrile solvate were grown from acetonitrile, and an X-ray structure was obtained (Figure 4). The absolute configuration of **33** was assigned as *R* at C2, C3, C5, C8, C10, C14, C17, C18, and C21; the conformations at C4, C13, and C34 were assigned as *S*.[16]

In conclusion, we have developed a practical, scaleable, and novel synthesis of glucan synthase inhibitors **1** and **2**. Notable features include a high-yielding ether bond formation between sulfamidate **17** and alcohol **4**, a highly efficient 5-step "through process" without isolation of intermediates for the synthesis of amide **8** from benzyl ester **20**, and a remarkable chemoselective, improved palladium(II)-mediated allylic oxidation by cumene hydroperoxide. Multi-hundred gram quantities of the target drug candidates **1** and **2** were synthesized in 12 linear steps with 25% isolated yield and 13 linear steps with 22% isolated yield, respectively.

EXPERIMENTAL SECTION

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-2-Hydroxy-3-methoxy-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradeca-hydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylic Acid (12).[5]
To a 100 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged enfumafungin **3** (4.000 kg, 5.643 mol) and dichloromethane (22.4 L). To the resulting slurry was charged triethylsilane (2.620 kg, 22.53 mol) in one portion. To the resulting mixture was slowly added TFA

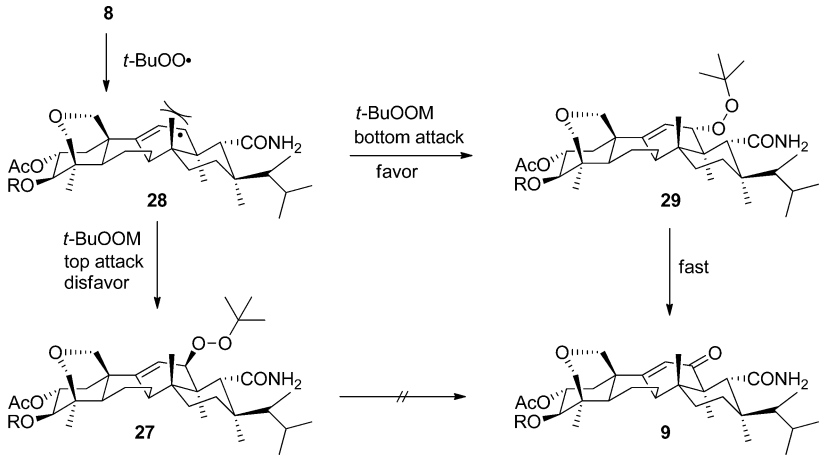

Figure 3. Proposed mechanism for the selectivity of allylic oxidation.

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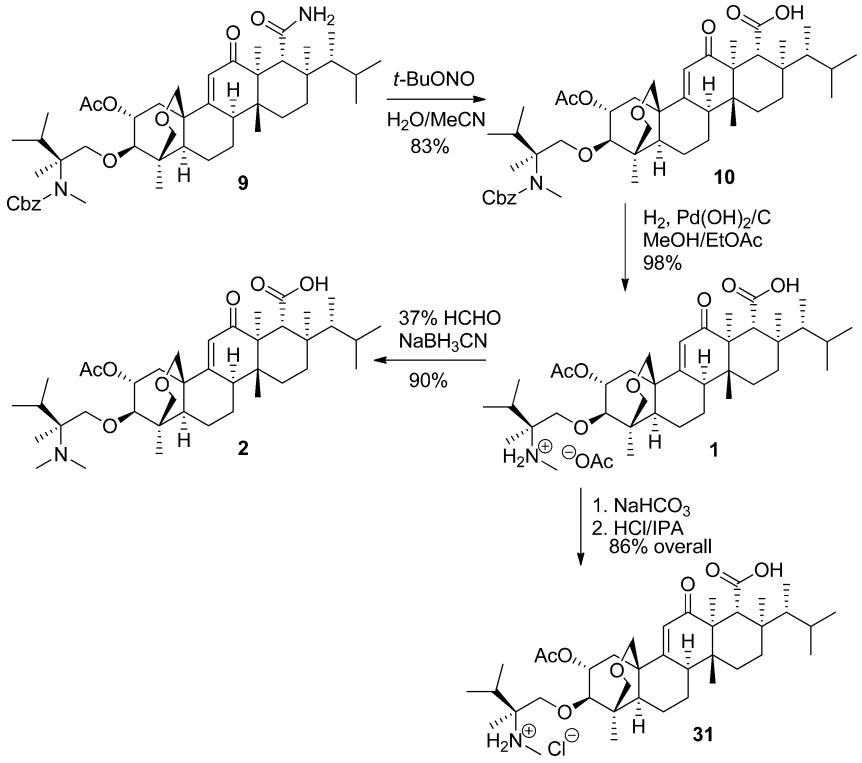
Scheme 6



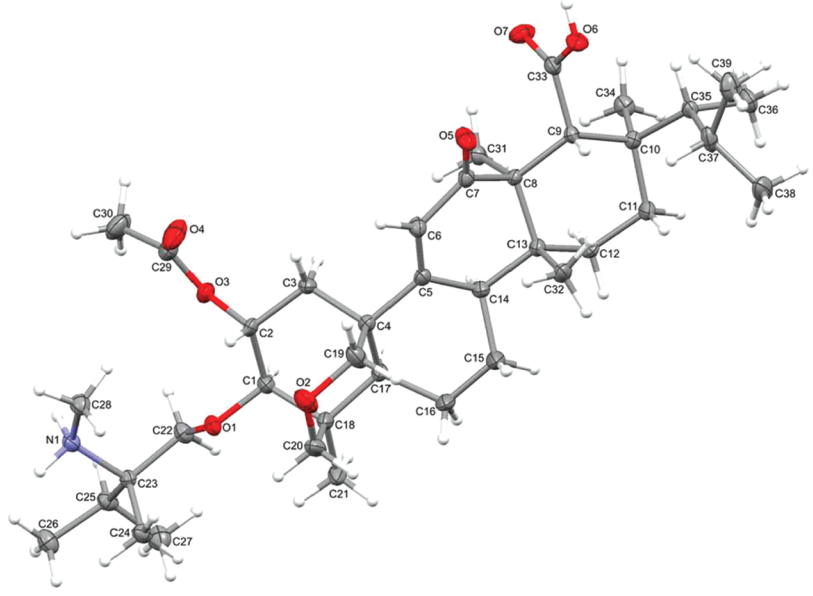


Figure 4. X-ray structure of compound **31**. The thermal ellipsoids represent 50% probability contours, while the H atoms are drawn at an arbitrary size. For clarity the water and acetonitrile solvent molecules along with the Cl counterion have been omitted.

(7.250 kg, 63.59 mol) over 35 min while maintaining the temperature <30 °C. The reaction mixture was stirred at rt for 0.5 h (>99% conversion).

The dichloromethane was concentrated to a low volume. To the solution was added methanol (2 × 11.2 L) and concentrated down to a low volume. To the resulting slurry was charged methanol (40 L) and then slowly 96% sulfuric acid (1.680 L, 30.26 mol) was added. The reaction flask was equipped with a condenser. The reaction mixture was refluxed for 14 h to form white slurry and then cooled to 6 °C. To the slurry was added cold water (40 L) over 10 min. The reaction mixture was stirred at 10 °C for 0.5−1 h. The crystalline solid was collected by filtration, washed by cold MeOH/water (1:1, 20 L), cold MeOH/3% NaOAc aqueous (1:1, 20 L), cold MeOH/water (1:1, 20 L), and heptanes (10 L) and dried under vacuum with nitrogen to afford acid **12** (2.548 kg, 90% isolated yield), mp 266.7−267.3 °C. $[\alpha]^{20}_{D}$ −73.0° (THF, c = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.46 (m, 1 H), 4.16 (m, 1 H), 3.77 (d, J = 11.5 Hz,1 H), 3.43 (s, 3 H), 3.31 (d, J = 11.5 Hz, 1 H), 3.18 (d, J = 8.5 Hz, 1 H), 2.86 (s, 1 H), 2.44 (dd, J = 13.3, 6.8 Hz, 1 H), 2.15 (m, 1 H), 2.03 (m, 1 H), 1.95 (m, 1 H), 1.82−1.70 (m, 3 H), 1.65−1.36 (m, 5 H), 1.25 (s, 3 H), 1.28−1.22 (overlapped, m, 4 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.80 (s, 3 H), 0.76 (d, J = 7.1 Hz, 3 H), 0.72 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 176.3, 143.4, 120.6, 82.0, 81.1, 72.7, 66.0, 58.2, 53.0, 48.5, 45.9, 41.2, 40.7, 40.3, 40.0, 39.2,

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38.4, 38.3, 38.2, 29.6, 28.7, 27.2, 25.9, 21.4, 19.8, 19.4 (2 C), 18.9, 17.2, 16.7, 9.1. HRMS (ESI) calculated for $C_{31}H_{50}O_5$: 503.3731 $(M + H)^+$, found 503.3725. Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 73.78; H, 9.86.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-Benzyl-2-hydroxy-3-methoxy-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylate (4).[5] To a 75 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged the acid **12** (2.600 kg, 5.172 mol), potassium carbonate powder (0.786 kg, 5.687 mol), and DMF (13 L, KF = 78 ppm). To the resulting slurry was then added benzyl bromide (0.973 kg, 5.690 mol) at 25−35 °C. The reaction mixture was then warmed to 78 °C over 0.5 h, and a complete conversion (>99%) was obtained.

The mixture was cooled to 17 °C by ice−water bath, and ethanol (6.0 L) was added. Then, water (9.0 L, 3.5 vol) was slowly added to the reaction mixture at 17 to 21 °C over 1 h. The resulting slurry was stirred at that temperature for 1 h. The crystalline solid was collected by filtration, washed with water/EtOH (1:1, 10 L), and dried under vacuum with nitrogen sweep for 48 h to afford 2.902 kg of the desired benzyl ester **4** (95% isolated yield) as white solid, mp 192.4−193.5 °C. $[\alpha]^{20}_D$ −36.5° ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.29 (m, 5 H), 5.41 (m, 1 H), 5.11 (d, J = 12.3 Hz, 1 H), 4.98 (d, J = 12.3 Hz, 1 H), 4.14 (m, 1 H), 3.77 (d, J = 11.8 Hz, 1 H), 3.43 (s, 3 H), 3.41−3.37 (m, 2 H), 3.30 (d, J = 11.8 Hz, 1 H), 3.17 (d, J = 8.6 Hz, 1 H), 2.87 (s, 1 H), 2.50−2.40 (m, 2 H), 2.11 (m, 1 H), 2.02 (br d, J = 13.0 Hz, 1 H), 1.92 (br d, J = 17.8 Hz, 1 H), 1.82−1.69 (m, 3 H), 1.60−1.34 (m, 5 H), 1.30−1.24 (m, 3 H), 1.23 (s, 3 H), 1.15 (m, 1 H), 1.14 (s, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.80 (s, 3 H), 0.77 (d, J = 6.8 Hz, 3 H), 0.72 (d, J = 7.1 Hz, 3 H), 0.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 141.8, 136.0, 128.5 (2 C), 128.4 (2 C), 128.0, 120.0, 80.9, 80.7, 72.1, 65.5, 65.1, 56.8, 52.6, 47.9, 43.8, 40.7, 40.0, 39.5, 38.3 (2 C), 38.2, 37.4, 37.2, 28.9, 27.8, 26.3, 24.6, 20.3, 18.7, 18.4, 18.3, 17.6, 16.3, 15.6, 8.0. HRMS (ESI) calculated for $C_{38}H_{56}O_5$: 610.4471 $(M + NH_4)^+$, found 610.4481. Anal. Calcd for $C_{38}H_{56}O_5$: C, 76.99; H, 9.52. Found: C, 76.69; H, 9.66.

(*S*)-2,3-Dimethyl-2-(methylamino)butan-1-ol (15).[17] To a 100 L four-neck round-bottom, equipped with an overhead stirrer, a thermocouple, and nitrogen inlet was charged 2 M $LiAlH_4$ in THF solution (16.4 L, 32.50 mol). The carbamate acid **14** (5.040 kg, 13.11 mol) in α-Me-THF and THF solution (8 L, total vol) was slowly added over 2 h and 25 min. The reduced reaction was exothermic. The reaction mixture was heated at 60 °C for 8 h.

Then, the reaction mixture was cooled to 5 °C. Water (1.5 L) was added dropwise over 3 h and 20 min at a temperature 18−24 °C. The addition was exothermic with vigorous gas generation! The reaction mixture turned to a thick white slurry. One normal NaOH aqueous (5 L, 25.00 mol) was added over 50 min at 20−24 °C, and the mixture was stirred for 10 min. The solid was filtered off and washed by THF (5 L × 5), with displacement wash by THF (5 L × 3), slurry wash by THF (10 L × 1), and displacement wash by THF (10 L × 1).

The combined filtrates were concentrated and flushed with α-Me-THF until the KF of the solution ≤400 ppm at a total volume 5.5 L. The solution was concentrated to an oil and cooled to crystallize. The resulting off white waxy solid was dried on a rotavapor and then high vacuum for 1.5 h to afford aminoalcohol **15** (1.610 kg, 94% yield) as a wax. $[\alpha]^{20}_D$ −7.5° (MeOH, c = 1.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37 (s, 2 H), 2.49 (broad s, 2 H), 2.27 (s, 3 H), 1.85 (m, 1 H), 0.91 (s, 3 H), 0.89 (d, J = 7 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.0, 58.5, 30.5, 27.5, 17.2, 16.9, 16.6. HRMS (ESI) calculated for $C_7H_{17}NO$: 132.1383 $(M + H)^+$, found 132.1380.

(*S*)-4-Isopropyl-3,4-dimethyl-1,2,3-oxathiazolidine 2,2-dioxide (17). To a 75 L four-neck round-bottom, equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged aminoalcohol (1.610 kg, 12.27 mol), dichloromethane (14.5 L), and DIEA (4.700 L, 26.99 mol). The resulting solution was cooled to −17 °C. Thionyl chloride (0.982 L, 13.50 mol) in dichloromehane (1.60 L) was added dropwise over 1.6 h at a temperature −8 to −4 °C. The reaction went from colorless to a deep red solution. The reaction mixture was stirred at −3 °C for 1 h (the reaction was monitored by ^{1}H NMR).

Water (8 L) was slowly added to the reaction mixture. After phase separation, the organic layer was washed by water (8 L × 1). The resulting crude sulfamidite intimidate was purified by passing through silica gel (8.30 kg) plug eluting with heptane/EtOAc (3:1) to give relative pure sulfamidite intermediate (1.980 kg).

To a 75 L four-neck round-bottom, equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged $NaIO_4$ (2.790 kg, 13.04 mol), acetonitrile (7.4 L), catalytic amount of $RuCl_3 \cdot xH_2O$ (0.0185 kg, 0.090 mol), and the mixture was cooled to 7 °C. Sulfamidite (1.980 kg) in acetonitrile (3 L) was slowly added to the reaction mixture over 1.6 h. The reaction was stirred at rt for about 1 h. (The reaction was monitored by ^{1}H NMR.)

The resulting slurry was diluted with IPAc (12 L) and water (4 L). Some insoluble solids were filtered off and washed by IPAc (12 L × 1). The combined filtrates were phase separated. The organic layer was washed by water (4 L × 1) and 15% brine (4 L × 1) and concentrated to give crude product sulfamidate **17** as a solid.

The crude sulfamidate **17** was dissolved in IPAc (2 L). Heptane (2 L) was slowly added and seeded to crystallize. To the resulting slurry was slowly added heptane (4 L) over 1 h, and the mixture was stirred at rt for 0.5 h. Then the slurry was stirred at 2−4 °C for 1.5 h. The crystalline solid was collected, washed with cold heptane/EtOAc (5:1, 2 L) and heptane (2 L), and dried under vacuum with nitrogen sweep to afford sulfamidate **17** (1.850 kg, 78% overall yield, > 97% ee), mp 58.9−59.6 °C. $[\alpha]^{20}_D$ −9.1° (MeOH, c = 0.91). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.38 (d, J = 8.8 Hz, 1 H), 4.06 (d, J = 8.8 Hz, 1 H), 2.65 (s, 3 H), 1.85 (m, 1 H), 1.32 (s, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 73.1, 65.5, 34.0, 26.5, 19.6, 16.8, 16.6. HRMS (ESI) calculated for $C_7H_{15}NO_3S$: 194.0845 $(M + H)^+$, found 194.0837. Anal. Calcd for $C_7H_{15}NO_3S$: C, 43.50; H, 7.82; N, 7.25. Found: C, 43.23; H, 7.95; N, 7.18.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-Benzyl 2-((*S*)-2,3-dimethyl-2- (methylamino)butoxy)-3-methoxy-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylate (19). To a 75 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged with sulfamidate **17** (1.063 kg, 5.500 mol) and ester **4** (2.711 kg, 4.573 mol) in toluene (29 L) were azotropically dried to provide a small volume of the toluene solution (<10 L, KF < 200 ppm). The required DMAc (20 L, KF = 78 ppm) was added to provide a solution (KF = 188 ppm) at room temperature.

To the above solution was slowly added potassium *tert*-pentoxide (PTP) solution (3.23 L, 5.500 mol) via an additional funnel at 20−25 °C over 0.5 h. The reaction mixture was stirred at rt for 24 h (100% conversion). IPAc (10 L) was added to the reaction mixture, followed by addition of 5 N HCl (3.3 L) and water (5.7 L). The resulting mixture was stirred for 0.5 h. Five normal NaOH (4 L) was added slowly to bring the pH to 11.2 as indicated by a pH meter. The mixture was transferred to a 100 L vessel. The 75 L round-bottom was rinsed with additional IPAc (14 L) and water (18 L) and then transferred to the 100 L vessel. After being stirred for ∼0.5 h, the aqueous layer was separated and then extracted with IPAc (25 L × 1). The combined IPAc layers were washed with 5% K_2CO_3 (18 L × 1) and then water (18 L × 2). The organic layer was collected and assayed by HPLC against to pure standard to give desired amine 19 (3.132 kg, 97% HPLC yield).

A small amount of the solution was concentrated and crystallized in IPAc to give crystalline **19**, mp 235.7−236.4 °C. $[\alpha]^{20}_D$ −34.5° ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39−7.30 (m, 5 H), 5.41 (m, 1 H), 5.11 (d, J = 12.3 Hz, 1 H), 4.98 (d, J = 12.3 Hz, 1 H), 4.15 (m, 1 H), 3.84 (d, J = 9.3 Hz, 1 H), 3.71 (d, J = 11.6 Hz, 1 H), 3.42−3.34 (m, 5 H), 3.27 (d, J = 11.6 Hz, 1 H), 2.87 (s, 1 H), 2.82 (d, J = 8.4 Hz, 1 H), 2.4 (dd, J = 13.4, 6.9 Hz, 1 H), 2.33 (s, 3 H), 2.11 (m, 1 H), 2.06 (m, 1 H), 1.93−1.80 (m, 2 H), 1.77−1.68 (m, 3 H), 1.59−1.34 (m, 5 H), 1.26−1.24 (m, 2 H), 1.23 (s, 3 H), 1.20−1.16 (m, 2 H), 1.15 (s, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.95 (s, 3 H), 0.90

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(d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.77 (s, 3 H), 0.72 (d, J = 6.5 Hz, 3 H), 0.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 142.1, 136.2, 128.7 (2 C, 128.5 (2 C), 128.2, 120.2, 88.4, 81.9, 74.8, 72.4, 66.2, 65.7, 56.4, 52.8, 48.1, 44.7, 40.8, 39.8, 39.7, 39.6, 38.4, 38.3, 37.5, 37.4, 31.5, 29.1, 28.1, 28.0, 26.5, 24.8, 21.9, 20.5, 19.1, 18.6, 18.4, 18.1, 17.6, 17.4, 17.0, 16.5, 15.8, 8.1. HRMS (ESI) calculated for $C_{45}H_{71}NO_5$: 706.5405 $(M + H)^+$, found 706.5415. Anal. Calcd for $C_{45}H_{71}NO_5$: C, 76.55; H, 10.14; N, 1.98. Found: C, 76.32; H, 10.25; N, 1.90.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-Benzyl 3-acetoxy-2-((*S*)-2,3-dimethyl-2-(methylamino)butoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylate (20). To a 50 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet was charged the IPAc solution of the amine **19** (3.132 kg, 4.436 mol) obtained from the previous step. The mixture was concentrated. When it was concentrated to a small volume (<8 L) at 20−25 °C, a light slurry was observed. After being stirred at rt for 2 days, slurry of crystalline amine **19** was obtained.

AcOH (8 L) was slowly fed in under the vacuum-distillation for the solvent switch. An acetic acid solution of amine **19** was obtained after additional AcOH was added (4 L and then 3.2 L) and assayed by HPLC against standard to be ∼20 wt % of the amine **19** (or ∼4 vol of AcOH, KF at 732 ppm). To the resulting solution was added solid TsOHc·H_2O (2.101 kg, 11.05 mol), followed by addition of Ac_2O (2.256 kg, 22.10 mol) at rt over 0.5 h to afford a clear solution (an increase of temperature from 19 to 30 °C was observed).

The solution was then heated to about 60 °C for 3 h. It was allowed to cool to rt and stirred overnight. A portion of AcOH (∼1/2 of AcOH added) was removed by distillation under vacuum at 18−30 °C, and the remaining mixture was diluted with IPAc (30 L) and then transferred to 100 L vessel. Additional IPAc (10 L) was used to rinse the 100-L RBF and then transferred.

The above solution was cooled to 20 °C, and 5 N NaOH was slowly added while maintaining the temperature at <25 °C until the pH 11.5 as indicated on a pH meter. The aqueous layer was separated, and the organic layer washed with 5 wt % K_2CO_3 (18 L × 1) and then water (16 L × 1). The IPAc layer was collected and assayed by HPLC against standard to give 3.150 kg of compound **20** (97% HPLC yield).

The resulting solution was concentrated and solvent-switched to MeCN to provide slurry of the product. It was concentrated down to ∼22 L of batch size (7 vol of MeCN). The resulting slurry was stirred at 20 °C for 0.5 h, and then water (5 L) was added over 1 h. The batch temperature was cooled to 10−14 °C. The slurry was stirred at 10−14 °C for 2 h. The second portion of water (4 L) was added at 10 °C over 0.5 h. The slurry was warmed to 17 °C and stirred for 1 h. The crystalline product **20** was collected by filtration, rinsed with the mixed solvents (1/2 MeCN/H_2O, 4 L × 2), and then dried in the filter pot under vacuum and with nitrogen sweep to provide 3.011 kg of a white solid **20** (90% overall isolated yield from compound **4**), mp 209.8−211.0 °C. $[\alpha]^{20}_D$ −25.3° (MeOH, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37−7.28 (m, 5 H), 5.71 (m, 1 H), 5.37 (m, 1 H), 5.11 (d, J = 12.2 Hz, 1 H), 4.93 (d, J = 12.2 Hz, 1 H), 3.72 (d, J = 11.7 Hz, 1 H), 3.62 (d, J = 8.8 Hz, 1 H), 3.46 (d, J = 11.6 Hz, 1 H), 3.35 (d, J = 11.6 Hz, 1 H), 3.33 (d, J = 8.7 Hz, 1 H), 3.28 (d, J = 11.7 Hz, 1 H), 3.02 (d, J = 8.8 Hz, 1 H), 2.85 (s, 1H), 2.46 (dd, J = 13.3, 7.1 Hz, 1 H), 2.22 (s, 3 H), 2.10 (m, 1 H), 2.01 (s, 3 H), 1.97 (m, 1 H), 1.88−1.67 (m, 6 H), 1.58−1.33 (m, 5 H), 1.26−1.20 (m, 6 H), 1.14 (m, 1 H), 1.12 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.87 (s, 3 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.80 (d, J = 6.8 Hz, 3 H), 0.78 (s, 3 H), 0.77 (d, J = 6.9 Hz, 3 H), 0.70 (d, J = 7.2 Hz, 3 H), 0.69 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 170.4, 141.3, 136.1, 128.7 (2 C), 128.5 (2 C), 128.2, 120.6, 86.5, 76.2, 75.3, 72.3, 66.0, 65.7, 57.7, 52.7, 48.1, 44.6, 40.8, 40.3, 40.0, 39.6, 38.7, 38.3, 37.5, 37.3, 31.8, 29.1, 28.3 (2 C), 28.0, 26.5, 24.8, 21.7, 20.5, 19.1, 18.5, 18.4, 18.0, 17.5, 17.0, 16.5, 15.7, 8.1. HRMS (ESI) calculated for $C_{46}H_{71}NO_6$: 734.5354 $(M + H)^+$, found 734.5364. Anal. Calcd for $C_{46}H_{71}NO_6$: C, 75.27; H, 9.75; N: 1.91. Found: C, 75.05; H, 9.82; N: 1.82.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-Benzyl-3-acetoxy-2-((*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylate (21). To a 1 L three-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged the acid **20** (50.00 g, 0.06811 mol), potassium carbonate powder (10.36 g, 0.07493 mol), and DMF (171 mL, KF = 78 ppm). To the resulting slurry was then added benzyl bromide (12.81 g, 0.07493 mol) at 25−35 °C. The reaction mixture was then warmed to 78 °C over 0.5 h, and a complete conversion (>99%) was obtained.

The mixture was cooled to 17 °C by ice−water bath, and ethanol (115 mL) was added. Then, water (175 mL, 3.5 vol) was slowly added to the reaction mixture at 17 to 21 °C over 1 h. The resulting slurry was stirred at that temperature for 1 h. The crystalline solid was collected by filtration, washed with water/EtOH (1:1, 192 mL), and dried under vacuum with nitrogen sweep for 48 h to afford desired benzyl ester **21** (57.94 g, 98% isolated yield) as white solid, mp 103.1−103.9 °C. $[\alpha]^{25}_D$ −50.8° (MeOH, c = 0.25). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.27 (m, 10 H), 5.67 (m, 1 H), 5.37 (m, 1 H), 5.11 (m, 2 H), 4.98 (d, J = 12.5 Hz, 1 H), 4.94 (d, J = 12.5 Hz, 1 H), 4.40 (m, 1 H), 3.72 (d, J = 11.7 Hz, 1 H), 3.47 (d, J = 11.9 Hz, 1 H), 3.43 (d, J = 8.8 Hz, 1 H), 3.34 (dd, J = 11.9, 2.0 Hz, 1 H), 3.28 (d, J = 11.7 Hz, 1 H), 2.99 (d, J = 9.2 Hz, 1 H), 2.96 (s, 3 H), 2.85 (s, 1 H), 2.81 (m, 1 H), 2.44 (dd, J = 13.2, 7.0 Hz, 1 H), 2.10 (m, 1 H), 2.07 (s, 3 H), 1.98 (m, 1 H), 1.86 (m, 1 H), 1.77−1.66 (m, 3 H), 1.53 (s, 3 H), 1.50−1.32 (m, 3 H), 1.29 (s, 3 H), 1.25−1.19 (overlapped, m, 2 H), 1.21 (s, 3 H), 1.17 (m, 1 H), 1.12 (s, 3 H), 0.81 (d, J = 7.0 Hz, 6 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.77 (d, J = 7.0 Hz, 3 H), 0.75 (s, 3 H), 0.71 (d, J = 7.1 Hz, 3 H), 0.69 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 170.6, 155.7, 141.2, 137.3, 136.0, 128.6 (2 C), 128.5 (2 C), 128.3 (2 C), 128.2, 127.8 (2 C), 127.6, 120.5, 86.0, 76.6, 75.8, 72.2, 66.3, 65.8, 65.6, 64.5, 52.5, 47.9, 44.5, 40.7, 40.2, 39.9, 39.6, 38.5, 38.2, 37.4, 37.2, 33.4, 30.7, 28.9, 27.8, 26.4, 24.7, 21.7, 20.4, 19.0, 18.4, 18.3, 17.8, 17.7, 17.2 (2 C), 16.4, 15.6, 8.0. HRMS (ESI) calculated for $C_{54}H_{77}NO_8$: 868.5722 $(M + H)^+$, found 868.5728. Anal. Calcd for $C_{54}H_{77}NO_8$: C, 74.70; H, 8.94; N: 1.67. Found: C, 74.88; H, 9.21; N: 1.58.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-Benzyl-3-acetoxy-2-((*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylate (23). To a 100 mL three-neck round-bottom flask equipped with an overhead stirrer, thermocouple, dropping funnel, and nitrogen inlet were charged alkene **21** (4.250 g, 4.891 mmol), propionitrile (50 mL), and potassium carbonate (0.169 g, 1.223 mmol), and the mixture was cooled to −30 °C. To the resulting solution were added 37 wt % $Pd(OH)_2$/C (0.2798 g, 15 mol %) and potassium carbonate powder (0.169 g, 25 mol %), respectively. Five molar *tert*-butyl hydroperoxide in acetonitrile (TBHP, 9.80 mL, 48.91 mmol) was added, and the mixture was stirred at −30 °C for 96 h. Then, 10 mol % of 37 wt % $Pd(OH)_2$/C (0.1666 g) and another portion of 5.0 M of TBHP (4.90 mL, 24.46 mmol) were added, respectively. The mixture was stirred at −30 °C for another 96 h. The third 5 equiv of 5.0 M of TBHP (4.90 mL, 24.46 mmol) was added, and the mixture was stirred at the same temperature for 96 h (58% conversion).

The catalyst was filtered off and washed by methylene chloride (22% HPLC yield against to standard). The filtrate was solvent-switched to MeOH (50 mL, total vol) at <10 °C. The resulting methanol solution was slowly added to a 25 wt % $Na_2S_2O_3$ (60 mL) aqueous solution until the excess oxidant has been quenched. The reaction mixture was extracted by toluene (30 mL × 2). The combined organic layer was washed with 16% brine (15 mL). The organic layer was concentrated and solvent-switched to heptane (10 mL, total vol).

The crude product was purified by Biotage (eluting with heptanes/MTBE = 100:0 to 5:1) to give desired product *N*-Cbz enone amide **23** (0.735 g, 17% isolated yield) as white solid, mp 110.2−111.1 °C. $[\alpha]^{25}_D$ −25.9° (MeOH, c = 0.29). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 (m, 2 H), 7.38−7.32 (m, 6 H), 7.31−7.27 (m, 2 H), 5.77 (d, J =

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2.4 Hz, 1 H), 5.70 (m, 1 H), 5.25 (d, J = 12.2 Hz, 1 H), 5.11 (d, J = 12.4 Hz, 1 H), 4.99 (d, J = 12.4 Hz, 1 H), 4.98 (d, J = 12.2 Hz, 1 H), 4.42 (m, 1 H), 3.76 (d, J = 11.7 Hz, 1 H), 3.53 (d, J = 11.4 Hz, 1 H), 3.44 (d, J = 8.6 Hz, 1 H), 3.40 (dd, J = 11.7, 2.2 Hz, 1 H), 3.28 (d, J = 11.4 Hz, 1 H), 3.12 (s, 1 H), 3.01 (d, J = 8.6 Hz, 1 H), 2.96 (s, 3 H), 2.81 (m, 1 H), 2.53−2.47 (m, 1 H), 2.15 (m, 1 H), 2.07 (s, 3 H), 1.87−1.80 (m, 4 H), 1.71 (s, 3 H), 1.70−1.61 (m, 2 H), 1.56 (m, 1 H), 1.46 (m, 1 H), 1.36−1.24 (overlapped, m, 4 H), 1.29 (s, 3 H), 1.09 (s, 3 H), 0.82 (d, J = 7.2 Hz, 6 H), 0.79_3 (s, 3 H), 0.79_1 (d, J = 6.8 Hz, 3 H), 0.78 (s, 3 H), 0.72 (d, J = 6.7 Hz, 3 H), 0.69 (d, J = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.9, 174.2, 170.3, 161.9, 155.7, 137.4, 136.4, 128.8 (2 C), 128.3 (2 C), 128.2 (2 C), 127.8, 127.7 (2 C), 127.6, 123.1, 85.7, 77.6, 75.0, 70.8, 66.4, 66.0, 65.9, 64.5, 52.4, 46.0, 45.2, 43.2, 41.8, 41.1, 41.0, 40.9, 39.9, 38.2, 33.4, 30.7, 27.3, 26.7, 26.5, 24.2, 21.6, 21.5, 18.7, 18.6, 18.2, 17.8, 17.7, 17.2 (2 C), 15.6, 15.4, 8.0. HRMS (ESI) calculated for $C_{54}H_{75}NO_9$: 882.5515 $(M + H)^+$, found 882.5520. Anal. Calcd for $C_{54}H_{75}NO_9$: C, 73.52; H, 8.57; N: 1.59. Found: C, 73.66; H, 8.56; N: 1.48.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-2-((*S*)-2,3-dimethyl-2-(methylamino)butoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,-11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)-chrysene-7-carboxylic Acid (24). To a 100 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged compound **20** (2.920 kg, 3.980 mol), THF (40 L), Et_3N (1.660 L, 11.94 mol), 10 wt % of 10 wt % wet Pd/C (0.292 kg), formic acid (0.450 L, 11.94 mol), and then THF (4 L for the rinse). The mixture was heated to 50 °C over 0.5 h. After 0.5 h of stirring at 50 °C for, an aliquot was removed and assayed by HPLC to show no compound **20** remained.

The mixture was cooled to 25 °C and then filtered through a pad of Solka Flock. The cake was washed with THF (10 L). The combined filtrate and wash was transferred to a 100 L vessel, and then toluene (29 L), water (8 L), and brine (8 L) were added. The mixture was stirred for 0.5 h, and then a two-layer system was obtained. The aqueous layer was cut and assayed by HPLC to show no amino acid **24**. The organic layer was obtained and assayed by HPLC against to standard to give amino acid **24** (2.520 kg, 98% HPLC yield). The resulting organic solution was used for the next step.

A small amount of the crude product was purified by chromatography on silica gel to afford pure amino acid **24** as white solid, mp 241.5−242.3 °C. $[\alpha]^{20}_D$ −83.3° (MeOH, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.12 (br s, 2 H), 5.75 (m, 1 H), 5.42 (br d, J = 5.2 Hz, 1 H), 3.72 (d, J = 10.2 Hz, 1 H), 3.70 (d, J = 11.6 Hz, 1 H), 3.46 (d, J = 10.2 Hz, 1 H), 3.45 (d, J = 11.7 Hz, 1 H), 3.37 (d, J = 11.6 Hz, 1 H), 3.30 (d, J = 11.7 Hz, 1 H), 3.14 (d, J = 8.8 Hz, 1 H), 2.73 (s, 1 H), 2.44 (dd, J = 13.3, 7.0 Hz, 1 H), 2.31 (s, 3 H), 2.20 (m, 1 H), 2.03 (s, 3 H), 2.00−1.95 (m, 3 H), 1.87 (m, 1 H), 1.80−1.630 (m, 4 H), 1.58−1.40 (m, 3 H), 1.39−1.27 (m, 2 H), 1.24 (s, 3 H), 1.23−1.19 (m, 5H), 1.15 (s, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 H, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.84 (s, 3 H), 0.82 (d, J = 6.7 Hz, 3 H), 0.74 (d, J = 7.1 Hz, 3 H), 0.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.5, 170.2, 141.0, 121.2, 87.0, 76.1, 75.2, 72.4, 67.7, 65.8, 53.4, 47.8, 44.5, 40.4, 40.3, 40.0, 39.8, 38.3, 37.7, 37.6, 31.6, 29.2, 28.1, 27.0, 26.5, 24.9, 21.9, 21.7, 21.5, 20.6, 19.3, 18.5, 18.0, 17.9, 17.7, 17.2, 16.8, 15.8, 8.1. HRMS (ESI) calculated for $C_{39}H_{65}NO_6$: 644.4885 $(M + H)^+$, found 644.4882. Anal. Calcd for $C_{39}H_{65}NO_6$: C, 72.74; H, 10.17; N: 2.18. Found: C, 72.42; H, 10.24; N: 2.14.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-2-((*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylic Acid (22). To a 100 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet were charged amino-acid **24** (2.520 kg, 3.910 mol), THF (10 L), toluene (2.5 L), 20 wt % K_2CO_3 (7.00 L, 11.73 mol), and CbzCl (1.450 L, 9.780 mol). THF (2.6 L) was used to rinse. The mixture was stirred at 20 °C for 3 h.

Then, 5 N NaOH solution was slowly added, and the mixture was stirred at 20 °C for 6 h. Five normal HCl was slowly added (gas evolution) so that the pH of the aqueous was <4. Toluene (25.2 L) was then added, and the layers were separated. The organic layer was concentrated and solvent-switch to toluene (8.4 L, total vol).

Next, cyclohexane (30 L) was added. The resulting solution was washed by DMSO/water (5:1, 10.8 L × 3). At this point, the benzyl alcohol byproduct was completely washed out. The organic solution was washed by water (14.4 L × 3) to remove all DMSO. Assay product in the organic solution by HPLC against standard was 2.980 kg (98% HPLC yield overall).

The organic solution was concentrated and solvent-switched to dichloromethane (48 L, total volume) which contains *N*-Cbz acid **22** (2.980 kg, c = 0.0621 kg/L). At this point, the ratio of product with toluene was 1:1.87 (mol ratio). There was no cyclohexane in the solution. The resulting dichloromethane solution was used for the ketene formation.

A small amount of the crude product **22** was purified by Biotage (eluting with hexanes/EtOAc = 100:0 to 75:25) to afford pure *N*-Cbz acid **22** as white solid, mp 150.1−151.0 °C. $[\alpha]^{20}_D$ −75.3° ($CHCl_3$, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.96 (br s, 1 H), 7.35−7.26 (m, 5 H), 5.67 (m, 1 H), 5.43 (m, 1 H), 5.10 (d, J = 12.5 Hz, 1 H), 4.98 (d, J = 12.5 Hz, 1 H), 4.38 (m, 1 H), 3.72 (d, J = 11.6 Hz, 1 H), 3.49 (d, J = 11.4 Hz, 1 H), 3.43 (d, J = 8.5 Hz, 1 H), 3.36 (d, J = 11.4 Hz, 1 H), 3.28 (d, J = 11.6 Hz, 1 H), 2.99 (d, J = 9.2 Hz, 1 H), 2.96 (s, 3 H), 2.83 (s, 1 H), 2.80 (m, 1 H), 2.46 (dd, J = 13.1, 7.6 Hz, 1 H), 2.14 (m, 1 H), 2.06 (s, 3 H), 2.02−1.89 (m, 2 H), 1.78−1.68 (m, 3 H), 1.62−1.34 (m, 5 H), 1.28 (s, 3 H), 1.26−1.20 (m, 4 H), 1.18 (s, 3 H), 1.13 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 6 H), 0.75 (d, J = 6.7 Hz, 3 H), 0.74 (s, 3 H), 0.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.5, 170.7, 155.7, 141.2, 137.3, 128.3 (2 C), 127.8 (2 C), 127.6, 120.5, 86.0, 76.6, 75.8, 72.1, 66.3, 65.8, 64.5, 52.3, 48.0, 44.5, 40.6, 40.3, 39.9, 39.6, 38.5, 37.7, 37.4, 37.1, 33.4, 30.7, 28.9, 27.8, 26.4, 24.8, 21.7, 20.4, 19.0, 18.4, 18.3, 17.8, 17.7, 17.2 (2 C), 16.4, 15.6, 8.1. HRMS (ESI) calculated for $C_{47}H_{71}NO_8$: 778.5252 $(M + H)^+$, found 778.5245. Anal. Calcd for $C_{47}H_{71}NO_8$: C, 72.55; H, 9.20; N: 1.80. Found: C, 72.63; H, 9.21; N: 1.70.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-2-((*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-7-carbamoyl-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-3-yl Acetate (8). To a 100 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, a condenser and a nitrogen inlet was charged 1.520 kg of *N*-Cbz acid **22** (1.960 mol) in dichloromethane solution (25.45 L, c = 0.06201 kg/L). EDC (1.880 kg, 9.800 mol) was added, and the mixture was aged at 35 °C overnight. Heating was stopped, and the reaction mixture was washed with 5% brine solution (25 L × 1). The organic layer was collected and assayed by HPLC against to pure standard to give ketene **26** (1.262 kg, 100% HPLC yield). The ketene dichloromethane solution was solvent-switched to toluene (12 L, total vol), and the resulting solution was used in the next step.

A small amount of the solution was purified by Biotage (eluting with heptanes/EtOAc = 100:0 to 60:40) to obtain pure ketene **26**, mp 152.7−153.6 °C. $[\alpha]^{20}_D$ −76.6° (MeOH, c = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.28 (m, 5 H), 5.70 (m, 1 H), 5.47 (m, 1 H), 5.12 (d, J = 12.5 Hz, 1 H), 5.00 (d, J = 12.5 Hz, 1 H), 4.41 (br d, J = 7.4 Hz, 1 H), 3.72 (d, J = 11.6 Hz, 1 H), 3.52 (d, J = 11.5 Hz, 1 H), 3.37 (dd, J = 11.6, 1.8 Hz, 1 H), 3.29 (d, J = 11.5 Hz, 1 H), 3.00 (d, J = 8.7 Hz, 1 H), 2.97 (s, 3 H), 2.82 (m, 1 H), 2.47 (dd, J = 13.3, 7.1 Hz, 1 H), 2.19 (m, 1 H), 2.08 (s, 3 H), 1.93−1.82 (m, 2 H), 1.79−1.62 (m, 6 H), 1.53 (m, 1 H), 1.44−1−41 (m, 2 H), 1.30 (s, 3 H), 1.25−1.15 (m, 10 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 6 H), 0.77 (s, 3 H), 0.72 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.2, 170.6, 155.8, 141.6, 137.5, 128.4 (2 C), 127.9 (2 C), 127.7, 123.4, 120.1, 86.2, 76.8, 75.8, 72.1, 67.2, 66.4, 65.9, 64.6, 48.2, 46.9, 44.8, 40.3, 40.0, 39.0, 38.9 (2 C), 36.4, 36.3, 36.1, 33.4, 30.8, 27.8, 27.7, 27.6, 27.5, 24.9, 24.6, 21.8, 18.9, 18.7, 17.9 (2 C), 17.3, 16.9, 8.7. HRMS (ESI) calculated for $C_{47}H_{69}NO_7$: 777.5418 $(M + NH_4)^+$, found 777.5415.

In a 10 gallon Banco reactor was charged the above 12 L of toluene solution of 1.262 kg of ketene. The solution was cooled to −10 °C, and 6 L of liquid NH_3 was added. The mixture was stirred at 40 °C

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and 190 psi for 24 h. After being cooled to 0 °C and slow careful venting, the mixture was transferred to a 50 L cylinder vessel and diluted with 16 L of toluene. The mixture was washed with DMSO/water (5:1, 5 L × 6). To the organic layer was added 3 L of EtOAc, and the mixture was then washed with water (5.5 L × 3). The organic layer was concentrated to 3 volumes and flushed with 2 volumes of toluene. Heptane (6 L) was added slowly, and the slurry was stirred for at rt 1 h. The crystalline solid was collected by filtration, washed with heptane/toluene (3:1, 3 L × 1), and dried under vacuum with N_2 sweep giving crystalline amide product **8** (1.356 kg, 89% isolated yield from intermediate **22**), mp 154.6−155.0 °C. $[\alpha]^{20}_D$ −76.6° (MeOH, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39−7.29 (m, 5 H), 5.70 (m, 1 H), 5.44 (s, 1 H), 5.37 (br s, 1 H), 5.33 (br s, 1 H), 5.13 (d, *J* = 12.5 Hz, 1 H), 5.01 (d, *J* = 12.5 Hz, 1 H), 4.40 (d, *J* = 5.7 Hz, 1 H), 3.74 (d, *J* = 11.6 Hz, 1 H), 3.50 (d, *J* = 11.5 Hz, 1 H), 3.46 (d, *J* = 8.6 Hz, 1 H), 3.38 (d, *J* = 11.5 Hz, 1 H), 3.30 (d, *J* = 11.6 Hz, 1 H), 3.02 (d, *J* = 8.6 Hz, 1 H), 2.99 (s, 3 H), 2.83 (m, 1 H), 2.50 (s, 1 H), 2.48 (dd, *J* = 13.3, 7.1 Hz, 1 H), 2.10 (s, 3 H), 2.08−2.04 (m, 2 H), 1.82−1.68 (m, 6 H), 1.61−1.44 (m, 3 H), 1.39−1.35 (m, 2 H), 1.31 (s, 3 H), 1.29−1.24 (m, 5 H), 1.22 (s, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 6 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.73 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.8, 170.9, 155.8, 141.6, 137.5, 128.4 (2C), 127.8 (2 C), 127.7, 120.5, 86.1, 76.7, 75.9, 72.4, 66.4, 65.9, 64.6, 52.7, 47.0, 44.5, 41.0, 40.3, 40.0, 39.7, 38.6, 37.9, 37.7, 37.6, 33.4, 30.9, 28.8, 27.8, 26.8, 24.9, 21.8, 20.7, 19.1, 18.7, 18.5, 17.9, 17.8, 17.4, 17.3, 16.1, 15.8, 8.3. HRMS (ESI) calculated for $C_{47}H_{72}N_2O_7$: 777.5412 $(M + H)^+$, found 777.5418. Anal. Calcd for $C_{47}H_{72}N_2O_7$: C, 72.64; H, 9.34; N: 3.60. Found: C, 72.98; H, 9.48; N: 3.43.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-2-((*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-7-carbamoyl-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-3-yl Acetate (9). To a 50 L cylinder vessel, equipped with an overhead stirrer, thermocouple, dropping funnel, and nitrogen inlet were charged dichloromethane (19.5 L) and amide **8** (1.158 kg, 1.489 mol), and the mixture was cooled to 0−5 °C. To the resulting solution was added 37 wt % $Pd(OH)_2/C$ (0.0567 kg, 10 mol %) and potassium carbonate powder (0.031 kg, 15 mol %), respectively. Cumene hydroperoxide (CHP, 88 wt %, 1.489 L, 6 equiv) was added, and the reaction mixture was aged at 0−5 °C for 22 h.

Five mole percent of 37 wt % $Pd(OH)_2/C$ (0.0283 kg) and another portion of cumene hydroperoxide (1.489 L, 6 equiv) was added and aged at the same temperature for 23 h. Then, 5.0 M TBHP in decane (1.49 L, 5 equiv) was added, and the solution was stirred at 0−5 °C for 23 h. Then, another 5 equiv of 5.0 M of TBHP (1.47 L) was added and aged for another 30 h. The third 5 equiv of 0.5 M TBHP (5 M, 1.47 L) was added and stirred at the same temperature for 23 h (>97% conversion).

The catalyst was filtered off and washed by methylene chloride (64% HPLC yield against to standard). The filtrate was solvent-switched to MeOH (12 L, total vol) at <10 °C, and 12 L of MeOH was added to the 50 L round-bottom before starting the solvent-switch.

The resulting methanol solution was slowly added to a 25 wt % $Na_2S_2O_3$ (47 L) aqueous solution until the excess oxidant has been quenched. The reaction mixture was extracted by toluene (12 L × 2). The combined organic layer was washed by 16% brine (6 L × 1). The organic layer was concentrated and solvent-switched to heptane (5.1 L, 0.754 kg of desired product **9** assayed by HPLC against to standard).

The crude product was purified by Biotage (eluting with heptanes/EtOAc = 100:0 to 2:1), and then further purified by reverse phase HPLC separation to give desired product *N*-Cbz enone amide **9** (0.573 kg, 49% isolated yield from intermediate **8**) as white solid, mp 152.2−153.3 °C. $[\alpha]^{20}_D$ −54.3° ($CHCl_3$, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39−7.30 (m, 5 H), 6.12 (br s, 1 H), 5.75 (d, *J* = 1.4 Hz, 1 H), 5.73 (m, 1 H), 5.25 (br s, 1 H), 5.13 (d, *J* = 12.5 Hz, 1 H), 5.01 (d, *J* = 12.5 Hz, 1 H), 4.45 (d, *J* = 6.4 Hz, 1 H), 3.79 (d, *J* = 11.7 Hz, 1 H), 3.56 (d, *J* = 11.5 Hz, 1 H), 3.46 (d, *J* = 8.3 Hz, 1 H), 3.41 (d, *J* = 11.5 Hz, 1 H), 3.30 (d, *J* = 11.7 Hz, 1 H), 3.23 (s, 1 H), 3.04 (d, *J* = 8.3 Hz, 1 H), 2.98 (s, 3 H), 2.83 (m, 1 H), 2.56−2.48 (m, 2 H), 2.10 (s, 3 H), 2.05 (m, 1 H), 1.90−1.80 (m, 2 H), 1.74−1.67 (m, 6 H), 1.65−1.48 (m, 4 H), 1.37−1.26 (m, 5 H), 1.21 (s, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 6 H), 0.81 (s, 3 H), 0.78 (s, 3 H), 0.77 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.1, 176.9, 170.4, 161.4, 155.2, 137.3, 128.3 (2 C), 127.7 (2 C), 127.5, 123.2, 85.6, 76.7, 75.0, 70.8, 66.3, 65.8, 64.4, 52.1, 49.3, 45.2, 44.7, 43.0, 42.3, 41.4, 40.8, 40.7, 39.9, 38.1, 33.3, 30.7, 27.4, 26.9, 26.7, 26.5, 24.4, 22.1, 21.6, 28.8, 18.6, 17.9, 17.8, 17.6, 17.1, 16.2, 16.0. HRMS (ESI) calculated for $C_{47}H_{70}N_2O_8$: 808.5473 $(M + NH_4)^+$, found 808.5476. Anal. Calcd for $C_{47}H_{70}N_2O_8$: C, 71.36; H, 8.92; N: 3.54. Found: C, 71.09; H, 8.93; N: 3.27.

(1*S*,2*R*,3*R*,4a*R*,6*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-2-((*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-7-carbamoyl-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-((2-phenylpropan-2-yl)peroxy)-2,3,4,6,6a,7,8,9,10,10a,-10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-3-yl Acetate (30). White solid, mp 129.5−130.3 °C. $[\alpha]^{25}_D$ −71.5° (MeOH, *c* = 0.33). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43−7.26 (m, 10 H), 5.83 (dd, *J* = 5.2, 2.1 Hz, 1 H), 5.74−5.69 (m, 2 H), 5.11 (m, 1 H), 5.02−4.98 (m, 2 H), 4.40 (m, 1 H), 3.80 (d, *J* = 5.2 Hz, 1 H), 3.75 (d, *J* = 11.6 Hz, 1 H), 3.53 (d, *J* = 12.0 Hz, 1 H), 3.44 (d, *J* = 8.6 Hz, 1 H), 3.39 (dd, *J* = 11.6, 2.1 Hz, 1 H), 3.29 (d, *J* = 12.0 Hz, 1 H), 3.21 (s, 1 H), 3.00 (d, *J* = 9.2 Hz, 1 H), 2.98 (s, 3 H), 2.81 (m, 1 H), 2.71 (s, 1 H), 2.52 (dd, *J* = 13.4, 7.5 Hz, 1 H), 2.09 (s, 3 H), 2.01 (d, *J* = 12.6 Hz, 1 H), 1.81−1.67 (m, 3 H), 1.61 (m, 1 H), 1.55 (s, 3 H), 1.49 (m, 1 H), 1.40−1.36 (m, 2 H), 1.30 (s, 3 H), 1.28−1.23 (m, 3 H), 1.22 (s, 3 H), 1.19 (s, 3 H), 1.15 (s, 3 H), 1.05 (m, 1 H), 0.82 (d, *J* = 7.0 Hz, 6 H), 0.78 (d, *J* = 7.2 Hz, 3 H), 0.76 (s, 3 H), 0.73 (d, *J* = 6.8 Hz, 3 H), 0.66 (d, *J* = 7.4 Hz, 3 H), 0.61 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.9, 170.4, 155.8, 144.6, 144.4, 137.4, 128.4 (2 C), 128.1 (2 C), 127.8 (2 C), 127.6 (2 C), 125.7 (2 C), 119.3, 85.9, 81.8, 81.1, 77.3, 75.7, 71.7, 66.4, 65.9, 64.6, 46.4, 44.8, 44.4, 43.2, 40.6, 40.3, 40.2, 40.1, 38.4, 36.8, 33.4, 30.8, 28.7, 28.2, 27.0, 26.8, 26.5, 25.7, 24.9, 22.0, 21.8, 19.0, 18.9, 18.6, 18.5, 17.9, 17.7, 17.6, 17.2, 7.8. HRMS (ESI) calculated for $C_{56}H_{82}N_2O_8$: 911.6144 $(M + H)^+$, found 911.6153.

(1*S*,2*R*,3*R*,4a*R*,6*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-2-((*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-6-(*tert*-butylperoxy)-7-carbamoyl-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-3-yl Acetate (27). White solid, mp 135.0−135.8 °C. $[\alpha]^{25}_D$ −89.5° (MeOH, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38−7.30 (m, 4 H), 7.28 (m, 1 H), 6.49 (s, 1 H), 5.80 (dd, *J* = 5.2, 2.1 Hz, 1 H), 5.70 (m, 1 H), 5.31 (s, 1 H), 5.12 (d, *J* = 12.4 Hz, 1 H), 4.98 (d, *J* = 12.4 Hz, 1 H), 4.40 (m, 1 H), 3.79 (d, *J* = 5.2 Hz, 1 H), 3.73 (d, *J* = 12.0 Hz, 1 H), 3.50 (d, *J* = 11.7 Hz, 1 H), 3.42 (d, *J* = 9.0 Hz, 1 H), 3.38 (dd, *J* = 12.0, 2.1 Hz, 1 H), 3.27 (d, *J* = 11.7 Hz, 1 H), 3.13 (s, 1 H), 2.99 (d, *J* = 9.0 Hz, 1 H), 2.96 (s, 3 H), 2.80 (m, 1 H), 2.50 (dd, *J* = 13.4, 7.5 Hz, 1 H), 2.08 (s, 3 H), 2.05 (m, 2 H), 1.81−1.67 (m, 3 H), 1.53−1.40 (m, 4 H), 1.34 (m, 1 H), 1.32 (s, 3 H), 1.28 (s, 3 H), 1.26−1.22 (m, 2 H), 1.20 (s, 9 H), 1.17 (s, 3 H), 1.13 (m, 1 H), 0.91 (d, *J* = 7.3 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 7.3 Hz, 6 H), 0.80 (s, 3 H), 0.76 (s, 3 H), 0.74 (d, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.7, 170.7, 155.7, 144.6, 137.4, 128.4 (2 C), 127.8 (2 C), 127.6, 119.9, 85.9, 81.2, 80.0, 76.7, 75.7, 71.6, 66.4, 65.9, 64.7, 47.0, 45.5, 44.4, 43.2, 40.7, 40.4, 40.2, 40.1, 38.4, 36.9, 33.4, 30.8, 28.8, 28.7, 27.0, 26.7 (3 C), 24.8, 21.9, 21.8, 19.0, 18.9, 18.6 (2 C), 17.9, 17.8, 17.7, 17.2 (2 C), 8.1. HRMS (ESI) calculated for $C_{51}H_{80}N_2O_8$: 849.5987 $(M + H)^+$, found 849.5980.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-2-((*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2,3-dimethylbutoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylic Acid (10). To a 50 L 4-neck round-bottom, equipped with an overhead stirrer, thermocouple, and nitrogen inlet were charged acetonitrile (15.0 L), enone amide **9** (0.6904 kg, 0.8727 mol), and water (0.300 L), and the mixture was warmed to 28 °C. To the resulting solution was slowly

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added 90 wt % *tert*-butyl nitrite (0.576 L, 5.00 equiv) at 28−35 °C (exothermic reaction), and the mixture was stirred at 28−35 °C for 0.5−1 h (typical >99% conversion).

The reaction mixture was concentrated to 3.75 L (total volume), and EtOAc (12 L) was added. The resulting solution was washed with 10% $NaHCO_3$ (4.5 L), water (4.5 L), and brine (4.5 L). The organic layer was concentrated and completely solvent-switched to acetonitrile (5.8 L, total volume). At this point, small amount of crystalline solid *N*-Cbz enone acid **10** was formed. The resulting slurry was stirred at 0−5 °C for 16 h. The crystalline solid was collected by filtration, rinsed by cold acetonitrile (0 °C), and dried under vacuum with nitrogen sweep to afford crystalline *N*-Cbz enone acid **10** (0.491 kg, 83% isolated yield) as colorless needles, mp 223.5−224.0 °C. $[\alpha]^{20}_{D}$ −66.2° ($CHCl_3$, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.61 (br s, 1 H), 7.39−7.28 (m, 5 H), 5.83 (d, *J* = 2.2 Hz, 1 H), 5.73 (m, 1 H), 5.13 (d, *J* = 12.5 Hz, 1 H), 5.01 (d, *J* = 12.5 Hz, 1 H), 4.45 (d, *J* = 6.5 Hz, 1 H), 3.79 (d, *J* = 11.7 Hz, 1 H), 3.58 (d, *J* = 11.4 Hz, 1 H), 3.47 (d, *J* = 8.5 Hz, 1 H), 3.44 (d, *J* = 12.5 Hz, 1 H), 3.31 (d, *J* = 11.7 Hz, 1 H), 3.20 (s, 1 H), 3.04 (d, *J* = 8.5 Hz, 1 H), 2.99 (s, 3 H), 2.83 (m, 1 H), 2.56−2.50 (m, 2 H), 2.20 (m, 1 H), 2.10 (s, 3 H), 1.91−1.83 (m, 3 H), 1.74−1.54 (m, 6 H), 1.52−1.48 (m, 2 H), 1.37−1.27 (m, 6 H), 1.16 (s, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 6 H), 0.81 (s, 6 H), 0.79 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 203.7, 177.2, 170.5, 162.3, 155.8, 137.4, 128.4 (2 C), 127.9 (2 C), 127.7, 123.1, 85.8, 76.9, 75.1, 70.8, 66.5, 66.0, 64.7, 52.3, 46.0, 44.7, 43.3, 42.0, 41.3, 41.0, 40.9, 40.0, 38.2, 33.4, 30.8, 27.2, 26.7 (2 C), 24.5, 21.8, 21.7, 21.6, 18.8, 18.7, 18.2, 17.9, 17.8, 17.3, 16.0, 15.6, 8.1. HRMS (ESI) calculated for $C_{47}H_{69}NO_9$: 792.5045 (M + H)$^+$, found 792.5038. Anal. Calcd for $C_{47}H_{69}NO_9$: C, 71.27; H, 8.78; N: 1.77. Found: C, 71.13; H, 9.00; N: 1.80.

(*S*)-1-(((1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-7-carboxy-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-2-yl)oxy)-*N*,2,3-trimethylbutan-2-aminium Acetate (1). To a 5 gallon vessel equipped with an overhead stirrer and thermocouple was charged enone acid **10** (0.6887 kg, 0.8838 mol) in EtOAc (5.20 L) and methanol (5.20 L). Twenty weight percent $Pd(OH)_2$/C (0.0344 kg, 5% mol) and acetic acid (0.146 L, 2.652 mol) were added, respectively. The resulting reaction mixture was hydrogened under 40 psi of H_2 at rt for 0.5−1 h (100% conversion).

The catalyst was filtered off by passing Solka Flock, washed by MeOH/EtOAc (1:1, 4.6 L). The combined filtrates (filtered through in-line filter) were solvent-switched to EtOAc (6.2 L, total volume). The product crystalline solid was formed during solvent-switched. Acetic acid (0.0731 L, 1.5 equiv) was added. The slurry was stirred at rt for 4 h. The crystalline solid was collected by filtration, washed by EtOAc (2.5 L × 1), dried under vacuum with wet nitrogen sweep to remove remaining EtOAc, and then dried nitrogen to afford crystalline salt **1** as colorless needles (0.607 kg, 98% isolated yield), mp 190.5−191.8 °C. $[\alpha]^{20}_{D}$ −101.8 (MeOH, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 5.80 (s, 1 H), 5.77 (m, 1 H), 5.48 (br s, 3 H), 3.78 (d, *J* = 9.0 Hz, 1 H), 3.77 (d, *J* = 11.9 Hz, 1 H), 3.61 (d, *J* = 9.7 Hz, 1 H), 3.54 (d, *J* = 11.3 Hz, 1 H), 3.44 (d, *J* = 11.3 Hz, 1 H), 3.31 (d, *J* = 11.9 Hz, 1 H), 3.15 (s, 1H), 3.07 (d, *J* = 9.0 Hz, 1 H), 2.54−2.50 (m, 2 H), 2.48 (s, 3 H), 2.23 (m, 1 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.99 (m, 1 H), 1.91−1.85 (m, 3 H), 1.73−1.65 (m, 5 H), 1.59−1.49 (m, 3 H), 1.34−1.24 (m, 3 H), 1.14 (s, 3 H), 1.12 (s, 3 H), 1.00−0.95 (m, 9 H), 0.88 (s, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.81 (s, 3 H), 1.55 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 204.0, 176.2, 173.6, 171.1, 164.2, 123.1, 86.8, 76.0, 75.8, 71.1, 66.4, 59.1, 52.6, 46.3, 45.1, 43.8, 42.3, 41.7, 41.6, 38.1, 32.5, 29.0, 27.6, 27.3, 27.1, 25.5, 22.9, 22.6, 22.5, 19.8, 19.2, 18.8, 18.5, 18.4, 18.2, 18.1, 16.6, 16.1, 9.1. HRMS (ESI) calculated for $C_{39}H_{63}NO_7$ [free amino acid, (M + H)$^+$]: 658.4677, found 658.4683. Anal. Calcd for $C_{41}H_{67}NO_9$: C, 68.59; H, 9.41; N: 1.95. Found: C, 68.27; H, 9.68; N: 1.86.

(1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-2-((*S*)-2-(dimethylamino)-2,3-dimethylbutoxy)-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysene-7-carboxylic Acid (2). To a 20 L four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, and a nitrogen inlet, was charged acetate salt (**1**) (0.3200 kg, 0.4410 mol) and MeCN/MeOH (5:1, 3.2 L). Then, acetic acid was added dropwise, and 37% formaldehyde aqueous solution (1.616 L, 11.03 mol) was added slowly. The reaction mixture was cooled to 15 °C, and then solid sodium cyanoborohydride (0.0550 kg, 0.8820 mol) was added in portions to maintain the internal temperature <20 °C. The reaction mixture was heterogeneous solution. The reaction mixture was stirred at rt for 20 h (100% conversion).

The reaction mixture was concentrated and solvent-switched to ethyl acetate (12 L, total vol). The resulting solution was washed by 5 wt % sodium bicarbonate (4.8 L × 2) and water (3.2 L × 4). The organic layer was concentrated and solvent-switched to IPA (1.92 L, total volume). Crystalline solid **2** was formed during the solvent-switch. Water (3.2 L) was slowly added over 1.5 h. The resulting slurry was aged at rt for 2 h. The crystalline solid was collected by filtration, washed by water/IPA (2:1, 1 L), and dried under vacuum with nitrogen sweep to afford crystalline free base **2** as colorless needles (0.267 kg, 90% yield), mp 217.0−218.0 °C. $[\alpha]^{20}_{D}$ −90.3° (MeOH, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 5.82 (s, 1 H), 5.73 (m, 1 H), 3.82 (d, *J* = 11.7 Hz, 1 H), 3.72 (d, *J* = 9.6 Hz, 1 H), 3.57 (d, *J* = 11.5 Hz, 1 H), 3.53 (d, *J* = 9.6 Hz, 1 H), 3.43 (d, *J* = 11.5 Hz, 1 H), 3.31 (d, *J* = 11.7 Hz, 1 H), 3.17 (s, 1H), 3.01 (d, *J* = 8.6 Hz, 1 H), 2.59−2.50 (m, 2 H), 2.36 (s, 6 H), 2.22 (m, 1 H), 2.09 (m, 1 H), 2.04 (s, 3 H), 1.90−1.81 (m, 3 H), 1.73−1.58 (m, 6 H), 1.55−1.48 (m, 2 H), 1.36−1.29 (m, 3 H), 1.14 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.92 (s, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.88−0.86 (m, 9 H), 0.81 (s, 3H), 0.77 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 203.6, 177.3, 170.2, 161.8, 123.2, 86.7, 75.7, 75.2, 70.9, 66.0, 62.2, 52.3, 45.8, 44.8, 43.3, 41.9, 41.2, 40.9, 40.8, 39.9, 39.1 (2C), 38.2, 30.4, 27.2, 26.7, 26.6, 25.4, 24.5, 21.9, 21.6, 18.9, 18.7, 18.2 (2 C), 17.3, 15.9, 15.6, 14.6, 8.1. HRMS (ESI) calculated for $C_{40}H_{65}NO_7$: 672.4834 (M + H)$^+$, found 672.4839. Anal. Calcd for $C_{40}H_{65}NO_7$: C, 71.50; H, 9.75; N: 2.08. Found: C, 71.36; H, 9.92; N: 1.97.

(*S*)-1-(((1*S*,2*R*,3*R*,4a*R*,6a*S*,7*R*,8*R*,10a*R*,10b*R*,12a*R*)-3-Acetoxy-7-carboxy-1,6a,8,10a-tetramethyl-8-((*R*)-3-methylbutan-2-yl)-6-oxo-2,3,4,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-1,4a-(methanooxymethano)chrysen-2-yl)oxy)-*N*,2,3-trimethylbutan-2-aminium Chloride (31). To a 250 mL four-neck round-bottom flask equipped with an overhead stirrer, a thermocouple, a dropping funnel, and nitrogen inlet were charged acetate salt **1** (5.410 g, 7.535 mmol) and 1:1 acetonitrile/water (80 mL). Sodium bicarbonate (0.6300 g, 7.535 mmol) in water (6.3 mL) was added dropwise at room temperature. The reaction mixture was stirred at rt for 2−3 h. EtOAc (100 mL) was charged. The phase was separated. The organic layer was washed with brine (25 mL × 2). The organic layer was concentrated, and water was azotropically removed (KF <200 ppm) by EtOAc. The solution was adjusted to 65 mL (total vol) with EtOAc. Acetonitrile (30 mL) was charged. To the resulting solution was added dropwise 3.9 N HCl in IPA (2.03 mL, 7.917 mmol) over 1 h. When half of the HCl in IPA solution was charged, the batch was seeded with crystalline **31** (20 mg). The resulting slurry was stirred at rt for 3−4 h. The crystalline HCl salt **31** was collected by filtration, rinsed with EtOAc, and dried under vacuum with nitrogen sweep to afford **31** (4.96 g, 95% isolated yield). The single crystal **31** was grown from MeCN/MeOH/EtOAc = 6:1:4, mp 241.0−242.1 °C. $[\alpha]^{25}_{D}$ −66.9° (MeOH, *c* = 1.0). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 9.54 (br s, 1 H), 9.17 (br s, 2 H), 5.89 (d, *J* = 2.0 Hz, 1 H), 5.76 (m, 1 H), 3.89−3.74 (m, 3 H), 3.52 (d, *J* = 11.7 Hz, 1 H), 3.36 (d, *J* = 11.7 Hz, 1 H), 3.28 (d, *J* = 12.3 Hz, 1 H), 3.16 (s, 1 H), 3.12 (dd, *J* = 10.7, 9.8 Hz, 1 H), 2.68 (s, 3 H), 2.62 (m, 1 H), 2.50 (m, 1 H), 2.27−2.17 (m, 2 H), 2.06 (s, 3 H), 2.10−2.03 (overlapped, m, 1 H), 1.90−1.76 (m, 3 H), 1.65 (s, 3 H), 1.67−1.61 (overlapped, m, 1 H), 1.56 (m, 1 H), 1.52−1.45 (m, 2 H), 1.31 (s, 3 H), 1.34−1.25 (m, 3 H), 1.11 (s, 3 H), 1.09 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.91 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.79 (s, 3 H), 0.75 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 204.2, 176.3, 170.3, 162.2, 123.2, 87.3, 75.3, 74.2, 70.7, 65.8, 64.3, 52.2, 45.8, 44.4, 43.0, 42.0, 41.2, 40.9, 40.8, 39.9, 38.3, 29.5, 27.6, 27.1, 26.6 (2 C), 24.5, 21.8,

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21.7, 18.7 (2 C), 18.4, 18.3, 17.2, 17.0, 16.1, 16.0, 15.6, 8.1. HRMS (ESI) calculated for $C_{39}H_{63}NO_7$ [free amino acid, $(M + H)^+$]: 658.4677, found 658.4671.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR, ^{13}C NMR spectra of new compounds, Table 4, and X-ray crystallographic data for compound **31** in CIF format (deposition code: CCDC 857543). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent progress and reviews, see: (a) Bauer, M.; Reinhart, K. *Int. J. Med. Microbiol.* **2010**, *300*, 411−413. (b) Cadwell, K.; Patel, K. K.; Maloney, N. S.; Liu, T.-C.; Ng, A. C. Y.; Storer, C. E.; Head, R. D.; Xavier, R.; Stappenbeck, T. S.; Virgin, H. W. *Cell* **2010**, *141*, 1135−1145. (c) Gullo, A.; Foti, A.; Murabito, P.; Li Volti, G.; Astuto, M.; Stissi, C.; Rubulotta, F.; Sanfilippo, F.; Santonocito, C.; Sganga, G.; Ristagno, G. *Frontiers Biosci.* **2010**, *E2*, 906−911. (d) Simon, N.; Decaudin, B.; Lannoy, D.; Odou, M. F.; De Broucker, M.; Barthelemy, C.; Poret, E.; Dubreuil, L.; Odou, P. *Pulm. Pharmacol. Ther.* **2010**, *23*, 324−326. (e) Yong, M. K.; Buising, K. L.; Cheng, A. C.; Thursky, K. A. *J. Antimicrob. Chemother.* **2010**, *65*, 1062−1069. (f) Rubio-Terres, C.; Grau, S. *Expert Opin. Ther. Pat.* **2010**, *11*, 877−887. (g) Chalmers, J. D.; Al-Khairalla, M.; Short, P. M.; Fardon, T. C.; Winter, J. H. *J. Antimicrob. Chemother.* **2010**, *65*, 608−618. (h) Kinnebrew, M. A.; Ubeda, C.; Zenewicz, L. A.; Smith, N.; Flavell, R. A.; Pamer, E. G. *J. Infect. Dis.* **2010**, *201*, 534−543. (i) Isaacs, D. *Curr. Opin. Infect. Dis.* **2008**, *21*, 246−250. (j) Zotchev, S. B. *Curr. Med. Chem.* **2003**, *10*, 211−223. (k) Shaw, Peter J. *J. Antimicrob. Chemother.* **2002**, *49*, 63−67.

(2) For selected recent progress and reviews, see: (a) Swoboda, S.; Lichtenstern, C.; Ober, M. C.; Taylor, L. A.; Stoerzinger, D.; Michel, A.; Brobeil, A.; Mieth, M.; Hofer, S.; Sonntag, H.-G.; Hoppe-Tichy, T.; Weigand, M. A. *Chemotherapy (Basel, Switz.)* **2009**, *55*, 418−424. (b) Zhu, A.; Xu, L. *Zhongguo Yaofang* **2009**, *20*, 2047−2049. (c) Hajare, A. A.; Mali, M. N.; Sarvagod, S.; Kurane, S.; Patwardhan, S.; Dange, A. S. *Asian J. Res. Chem* **2009**, *2*, 213−219. (d) Maschmeyer, G.; Calandra, T.; Singh, N.; Wiley, J.; Perfect, J. *Med. Mycol.* **2009**, *47* (6), 571−583. (e) Aikawa, N.; Kusachi, S.; Oda, S.; Takesue, Y.; Tanaka, H. *J. Infect. Chemother.* **2009**, *15*, 219−227. (f) Brueggemann, R. J. M.; Alffenaar, J.-W. C.; Blijlevens, N. M. A.; Billaud, E. M.; Kosterink, J. G. W.; Verweij, P. E.; Burger, D. M. *Clin. Infect. Dis.* **2009**, *48*, 1441−1458. (g) Cannon, R. D.; Lamping, E.; Holmes, A. R.; Niimi, K.; Baret, P. V.; Keniya, M. V.; Tanabe, K.; Niimi, M.; Goffeau, A.; Monk, B. C. *Clin. Microbiol. Rev.* **2009**, *22*, 291−321. (h) Damle, B. D.; Dowell, J. A.; Walsky, R. L.; Weber, G. L.; Stogniew, M.; Inskeep, P. B. *Antimicrob. Agents Chemother.* **2009**, *53*, 1149−1156. (i) Gautam, P.; Shankar, J.; Madan, T.; Sirdeshmukh, R.; Sundaram, C. S.; Gade, W. N.; Basir, S. F.; Sarma, P. U. *Antimicrob. Agents Chemother.* **2008**, *52*, 4220−4227. (j) Maschmeyer, G.; Haas, A. *Future Microbiol.* **2006**, *1*, 365−385.

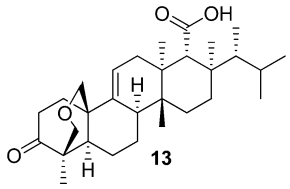
(3) Schwartz, R. E.; Smith, S. K.; Onishi, J. C.; Meinz, M.; Kurtz, M.; Giacobbe, R. A.; Wilson, K. E.; Liesch, J.; Zink, D.; Horn, W.; Morris, S.; Cabello, A.; Vicente, F. *J. Am. Chem. Soc.* **2000**, *122*, 4882−4886.

(4) (a) Pelaez, F.; Cabello, A.; Platas, G.; Diez, M. T.; Gonzalez del Val, A.; Basilio, A.; Martan, I.; Vicente, F.; Bills, G. E.; Giacobbe, R. A.; Schwartz, R. E.; Onish, J. C.; Meinz, M. S.; Abruzzo, G. K.; Flattery, A. M.; Kong, L.; Kurtz, M. B. *Systematic Appl. Microbiol.* **2000**, *23*, 333−43. (b) Onishi, J.; Meinz, M.; Thompson, J.; Curotto, J.; Dreikorn, S.; Rosenbach, M.; Douglas, C.; Abruzzo, G.; Flattery, A.; Kong, L.; Cabello, A.; Vicente, F.; Pelaez, F.; Diez, M. T.; Martin, I.; Bills, G.; Giacobbe, R.; Dombrowski, A.; Schwartz, R.; Morris, S.; Harris, G.; Tsipouras, A.; Wilson, K.; Kurtz, M. B. *Antimicrob. Agents Chemother.* **2000**, *44*, 368−77.

(5) (a) Greenlee, M. L.; Meng, D.; Mamai, A.; Fan, W.; Balkovec, J. M.; Peel, M.; Li, K. Antifungal agents. PCT Int. Appl. WO 2007126900, 2007. (b) Balkovec, J. M.; Boufford, F. A.; Tsu, B.; Dropinski, J.; Meng, D.; Greenlee, M. L.; Peel, M.; Fan, W.; Mamai, A.; Liu, H.; Li, K. Antifungal agents. PCT Int. Appl. WO 2007127012, 2007. (c) Balkovec, J. M.; Siliphaivanh, P.; Bouffard, F. A.; Peel, M. R.; Fan, W.; Mamai, A.; Dimick G.; Ray, S. M. Antifungal agents. PCT Int. Appl. WO 2009045311, 2009.

(6) (a) Joshi, D. K.; Sutton, J. W.; Carver, S.; Blanchard, J. P. *Org. Process Res. Dev.* **2005**, *9*, 997−1002. (b) Costanzo, M. J.; Patel, M. N.; Petersen, K. A.; Vogt, P. F. *Tetrahedron Let* **2009**, *50*, 5463−5466.

(7) The main degradation byproduct was the corresponding 3-ketone **13**.



13

(8) For example: methyl or benzyl esters of **12** can not be hydrolyzed to the corresponding carboxylic acid **12** by typical conditions such as LiOH, NaOH, or KOH in THF/water or MeOH/water.

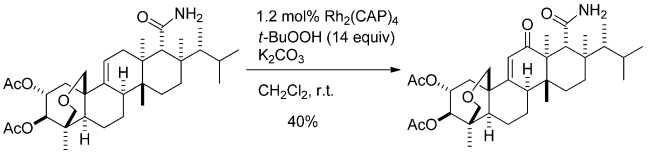
(9) For a review, see: Melendez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581.

(10) Kuethe, J. T.; Gauthier, D. R. Jr.; Beutner, G. L.; Yasuda, N. *J. Org. Chem.* **2007**, *72*, 7469−7472.

(11) For selected recent progress and reviews, see: (a) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128−2131. (b) Jiang, D.; Mallat, T.; Meier, D. M.; Urakawa, A.; Baiker, A. *J. Catal.* **2010**, *270*, 26−33. (c) Li, Y.; Wu, X.; Lee, T. B.; Isbell, E. K.; Parish, E. J.; Gorden, A. E. V. *J. Org. Chem.* **2010**, *75*, 1807−1810. (d) Yin, C.; Yang, Z.; Li, B.; Zhang, F.; Wang, J.; Ou, E. *Catal. Lett.* **2009**, *131*, 440−443. (e) Tan, Q.; Hayashi, M. *Adv. Synth. Catal.* **2008**, *350*, 2639−2644. (f) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730−738. (g) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349−5352. (h) McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317−4319. (i) Brasholz, M.; Reissig, H.-U. *Synlett* **2007**, 1294−1298. (j) Salvador, J. A. R.; Silvestre, S. M.; Moreira, V. M. *Curr. Org. Chem.* **2006**, *10*, 2227−2257. (k) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L *Org. Lett.* **2006**, *8*, 3149−3151. (l) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A: Chem.* **2006**, *250*, 70−74. (m) Salvador, J. A. R.; Silvestre, S. M. *Tetrahedron Lett.* **2005**, *46*, 2581−2584. (n) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. (o) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (p) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622−13623. (q) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407. (r) Humphyrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (s) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (t) Liu, J.; Wang, F.; Ma, Z.; Lin, J.; Gu, Z. *Catal. Commun.* **2011**, *15*, 103−107. (u) Catir, M.; Kilic, H. *Synlett* **2010**, 1319−1322. (v) The allylic oxidation of the benzyl ester **21**, and acid **22** and was also screened in microscale format (~400 reactions total, 2

mg scale). Supported metals (Pd, Pt, Rh, Ru) and their associated oxides were screened, along with salts of Mn, Ru, Cr, and Cu in various oxidation states in combination with several oxidants (TBHP, $BzOO^tBu$, MnO_2, BQ, O_2), all arrayed against solvents of varying polarity (e.g., heptane, Toluene, $PhCF_3$, DCM, EtOAc, MeCN).

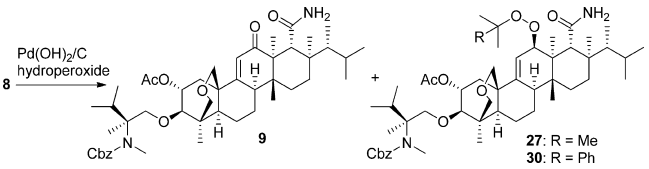
(12) Allylic oxidation for the model studies:



(13) It was noticed that ketene **26** is surprisingly stable and does not react with alcohols even at elevated temperature. When the crude acid **22**, containing 1 equiv of BnOH and some dibenzyl carbonate, was treated with EDC, only the corresponding benzyl ester was isolated in high yield. It is interesting to note that ketene **26** did not react with an excess amount of benzyl alcohol even at elevated temperature. Since the same EDC reaction with isolated acid **22** and $Me^{17}OH$ provided the clean ^{17}O labeled methyl ester, it was confirmed that an activated carboxylic acid with EDC reacted with alcohol not due to activation of alcohol. Thus, excess BnOH had to be removed from the crude acid mixture prior to formation of ketene. We found that benzyl alcohol could be removed completely by three DMSO/water (5:1) washes of the reaction mixture in cyclohexane without any loss of compound **22**. Then, without any further purification, compound **22** in cyclohexane was concentrated and the residue was dissolved in dichloromethane, and then treated with EDC at 35 °C to generate ketene **26**. The ketene was subsequently reacted with excess ammonia in toluene in the autoclave at 40 °C to afford colorless crystalline amide **8** in 89% isolated yield.

(14) (a) Tang, Y.; Dong, Y.; Wang, X.; Sriraghavan, K.; Wood, J. K.; Vennerstrom, J. L. *J. Org. Chem.* **2005**, *70*, 5103−5110. (b) Rigaudy, J.; Chelu, G.; Cuong, N. K. *J. Org. Chem.* **1985**, *50*, 4474−4478. (c) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730−738. (d) Ahn, Y. M.; Velde, D. G. V.; Georg, G. I. *J. Org. Chem.* **2002**, *67*, 7140−7143. (e) Yoshida, J.; Nakatani, S.; Sakaguchi, K.; Isoe, S. *J. Org. Chem.* **1989**, *54*, 3383−3389. (f) Muzart, J. *Tetrahedron Lett.* **1986**, *27*, 3139−3142.

(15) Optimization for the palladium-mediated allylic oxidation of amide **8** (for details, see the Supporting Information):



(16) The dihedral angle of the carbon−carbon double bond and the carbonyl, C9−C11−C12−O5, is −168.2°. This deviation from 180° of 11.8° is somewhat larger than is commonly observed in similar moieties in the Cambridge Structural Database (0° to 8°); however, there are several similar structures that show deviations of up to 18°. With this broad of a range of observations it is difficult to draw conclusions about the significance, if any, of the twist in this torsion angle away from 180°. We do note that this enone is not stable under strong acidic or strong basic conditions.

(17) Greenlee, M. L.; Wilkening, R.; Apgar, J.; Wildonger, K. J.; Meng, D.; Parker, D. L.; Mamai, A. Preparation of enfumafungin aglycon derivatives as antifungal agents, *PCT Int. Appl.*, 2010.