JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

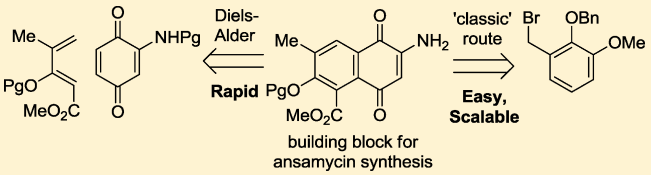
Two Approaches to the Aromatic Core of the Aminonaphthoquinone Antibiotics

Christopher C. Nawrat,† Leoni I. Palmer,† Alexander J. Blake, and Christopher J. Moody*

School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

Supporting Information

ABSTRACT: Two complementary approaches are presented for the synthesis of the quinone chromophores of the naphthoquinone ansamycins and related natural products. The first involves the use of an improved protocol for the manganese(III) acetate mediated cyclization of 5-aryl-1,3-dicarbonyl compounds to *β*-naphthols, leading to the simple, scalable preparation of building blocks suitable for the synthesis of naturally occurring aminonaphthoquinones. The second approach involves the Diels–Alder reaction of a series of new, ester-containing Danishefsky-type dienes with *N*-protected aminobenzoquinones to allow more expeditious access to similar intermediates.



INTRODUCTION

Aminonaphthoquinones are found at the core of a number of commercially and medicinally important natural products and their derivatives (Figure 1).[1] For example, rifabutin (**2**), a semisynthetic derivative of rifamycin S (**1**), is a current frontline antibiotic used for the treatment of multidrug resistant tuberculosis,[2,3] and other members of the rifamycin family exhibit various useful biological activities. In addition to these well-known examples, new members of this class of compounds continue to be reported in the literature; for example, the recently isolated natural products hygrocin A (**3**) and salinisporamycin (**4**) exhibit anticancer and antibiotic activity, respectively.[4,5] Given the historic importance of compounds of this type, chemistry that facilitates rapid access to these natural products is desirable. For this reason, a number of methods for the synthesis of the *ansa* chains of various ansamycins have been reported,[6−14] and new methods for the synthesis of polyketide and polypropionate subunits frequently appear in the literature.[15,16] However, the synthesis of the aminonaphthoquinone cores of these compounds still tends to use lengthy sequences of classical aromatic chemistry that have changed very little over the past 40 years. For example, Kishi's synthesis of the aromatic core of rifamycin S (**1**) required 16 linear steps from commercial starting materials, and a more recent approach toward the core of the divergolides by Rasapalli took over 12 steps, relatively lengthy routes to reach fairly simple substituted naphthalenes.[17−19] We now report two complementary approaches suitable for more rapid access to the naphthoquinone chromophores of this important class of molecules.

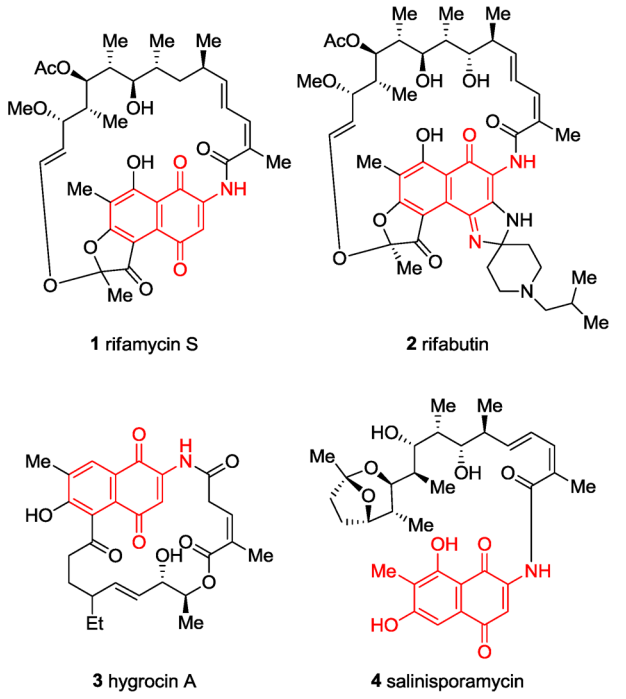


Figure 1. Some naturally occurring aminonaphthoquinones and their derivatives.

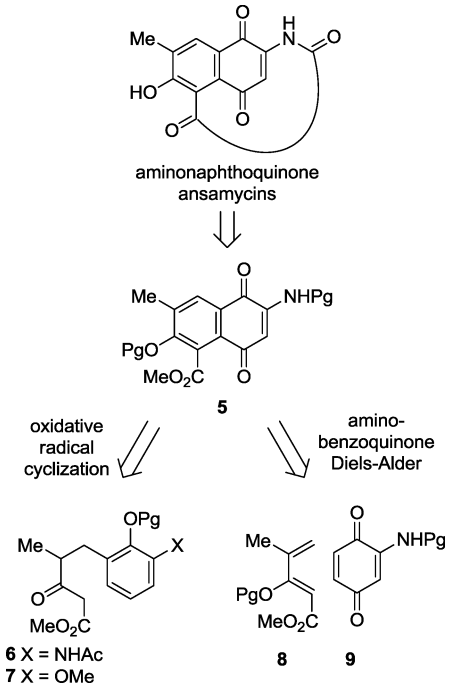
RESULTS AND DISCUSSION

Recently, during our studies on various ansamycin antibiotics, we required a rapid route to the quinone chromophores of these compounds. Depending on the method used for the attachment of the *ansa* chain, two similar precursors to these core structures could be imagined (Scheme 1). A naphthoquinone ester such as **5** would be a versatile precursor to the naphthoquinone ansamycins allowing the *ansa* chain to either

Received: April 8, 2013
Published: May 9, 2013

   dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

Scheme 1. Disconnections for the Aminonaphthoquinone Chromophore of the Ansamycins (Pg = Protecting Group)



be attached first at the ester position or by amide formation at the aminonaphthoquinone, giving a number of options for the order of bond formation in construction of the macrolactam ring. Initially, it was decided to approach ester **5** using the biomimetic oxidative radical cyclization developed by Rickards and Citterio on a β-ketoester such as **6** or **7**.[20,21] A second, complementary, approach to this same target can also be envisioned on the basis of a Diels–Alder reaction between a suitable diene **8** and an aminobenzoquinone dienophile **9**.[22]

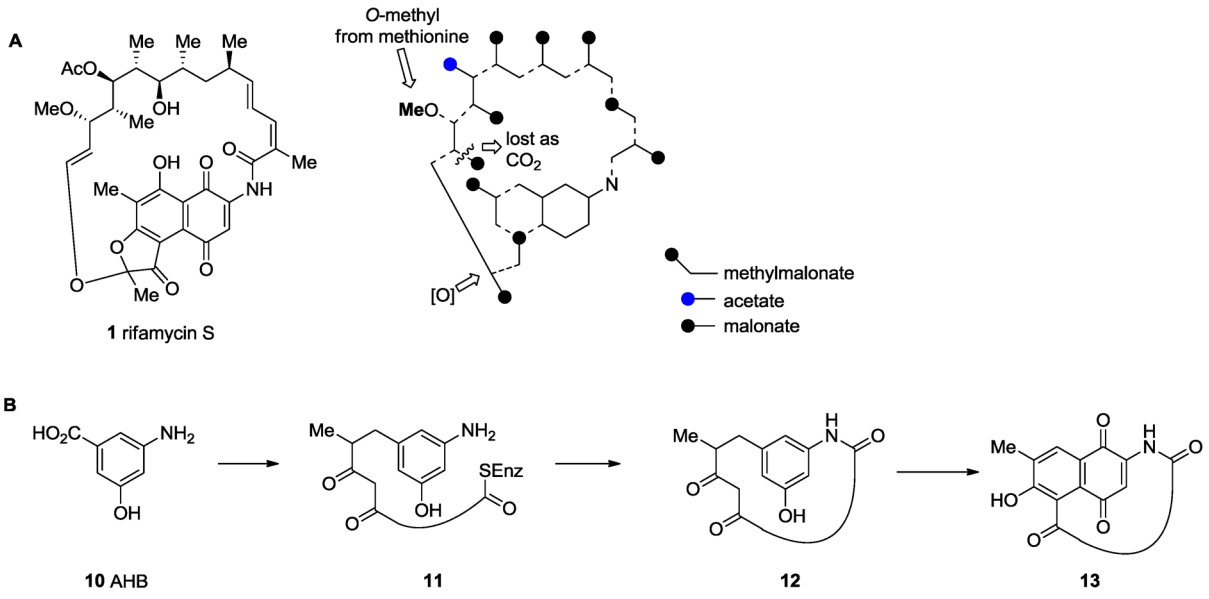
It has been shown that ansamycins are derived in Nature from 3-amino-5-hydroxybenzoic acid (**10**) (AHB),[23,24] and labeling studies have been used to determine the biosynthetic precursors to the entire carbon skeleton of rifamycin S (**1**) (Scheme 2A).[25,26] A biosynthetic proposal put forward by Rickards suggested that the rifamycin polyketide chain is attached first at the AHB carboxylic acid to give diketone **11** and that amide formation occurs later to give macrolactam **12** (Scheme 2B). The naphthoquinone nucleus is then formed by oxidation of phenol **12** to the quinone, followed by Michael addition of the readily enolized diketone and reoxidation to **13**.[27]

Some studies toward this end have already been carried out by Rickards, Citterio and others,[20,21] but the yields remain low, and the precursors themselves often require lengthy synthetic routes (Scheme 3). Thus, although Rickards successfully demonstrated the pseudobiomimetic oxidative cyclization of acetanilide **14** to naphthalene **15** in good yield (Scheme 3A), this precursor took nine steps to prepare from 3,5-dihydroxybenzoic acid and was obtained in low overall yield (<15%). The catechol derivative **16** (Scheme 3B) is more readily available, being preparable from *o*-vanillin in five steps, but the overall yield for the key cyclization and aromatization steps to give naphthalene **18** via tetralone **17** is considerably lower (16 vs 74%).

We began our studies toward naphthoquinone ester **5** by synthesizing a range of new β-ketoesters precursors for the oxidative cyclization reaction in the hope of finding a more readily accessible substrate for this reaction than those previously reported by Rickards (Scheme 4). This involved reaction of the dianion of methyl propionylacetate with the known benzyl bromides **19**,[21] **21**,[28,29] and **23**[21] to give the β-ketoesters **20**, **22**, and **24** in generally high yields (see the Experimental Section for details of improved routes to benzyl bromides **19** and **21**).

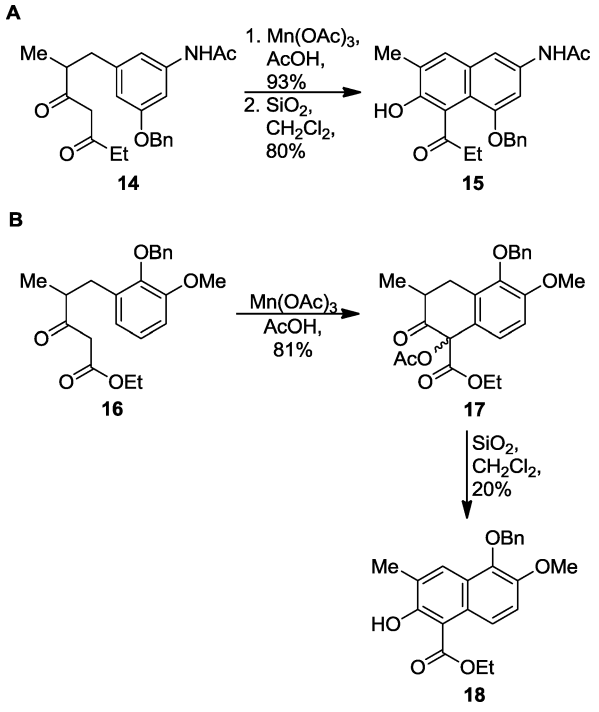
First, cyclization of the β-ketoesters was attempted using Fremy's salt in acetone/phosphate buffer under the conditions previously described by Rickards for the corresponding 1,3-diketones.[27] Surprisingly, given the generally high yields reported for this reaction on various 1,3-diketones in the

Scheme 2. (A) Results of Labeling Studies Carried out on Rifamycin S; (B)Rickards' Biosynthetic Proposal for the Naphthoquinone Ansamycins

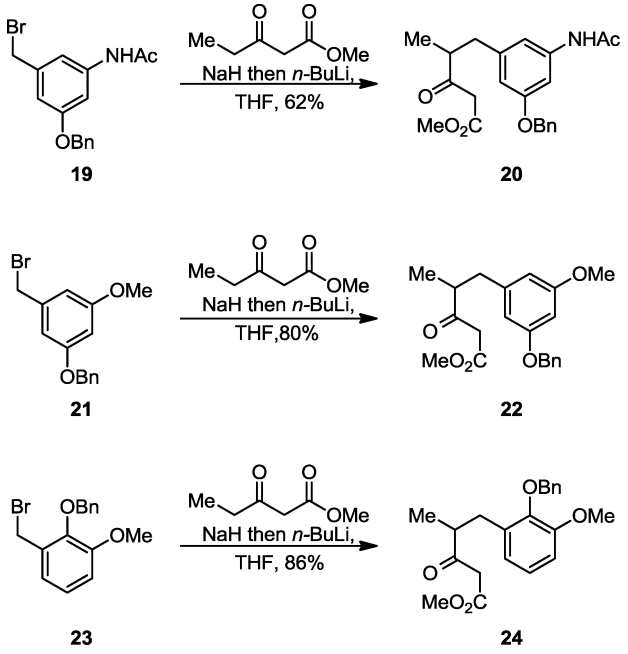


dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

Scheme 3. Rickards' Biomimetic Approach to the Core of the Naphthoquinone Ansamycins[21]

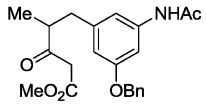
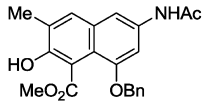
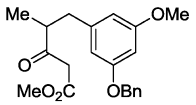
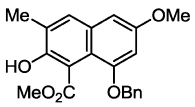
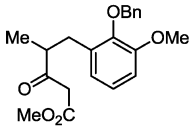
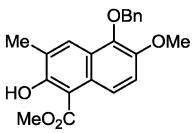


Scheme 4. Preparation of 5-Aryl-3-oxopentanoate Oxidative Cyclization Precursors



literature, and our own studies, only a trace of naphthoquinones was obtained for the β-ketoesters. This is presumably due to the lower acidity of the methylene group in this compound and hence the greater difficulty associated with formation of the enol required for cyclization to occur. In light of the apparent failure of this cyclization method when applied to β-ketoesters, we turned to the use of manganese(III) acetate as the oxidant, as this does not rely on enolization for cyclization to occur and is well precedented in this context (Scheme 3B).[27] Next, acetanilide **20**, containing a β-ketoester, was investigated, so that its reactivity could be compared to the corresponding 1,3-diketone **14** reported by Rickards. This change in functionality did not significantly affect the reactivity, and after cyclization and aromatization, we obtained β-naphthol **25** in essentially the same yield as had been reported for cyclization of diketone **14**. Protected resorcinol **22** was then prepared so its reactivity could be compared to the protected catechol **16** used by Rickards. Surprisingly, altering the position of the benzyloxy group had a dramatic effect on the reactivity of these substrates, and while **16** reportedly cyclized in an excellent yield of 81% when treated with manganese(III) acetate, our substrate **22** gave a markedly lower yield of 40% yield under the same conditions. Our yield for the aromatization of the initial cyclization product of **22** (19%) was comparable to that obtained by Rickards for the aromatization of **17** into **18** (20%). However, we had been using the aromatization conditions reported by Citterio (i.e., heating with silica under reflux in benzene),[20] whereas Rickards had employed basic silica (pH 10) in dichloromethane in his studies. Both steps for the conversion of **22** into naphthalene **26** were poor (Table 1),

Table 1. Preparation of Ester Precursors[a]

Substrate	Product	Yield/%
 **20**	 **25**	83%
 **22**	 **26**	8%
 **24**	 **27**	83%

[a]Oxidative cyclization was performed by treatment with $Mn(OAc)_3$ and AcOH followed by aromatization by reflux with silica in benzene (yields over two steps).

but sufficient material could be produced to confirm the structure of **26** by X-ray crystallography (see the Supporting Information). In view of this, we re-examined the possibility of using the known naphthoate ester **18** instead. Rickards has previously shown that β-ketoester **16** cyclizes efficiently into **17**, but the low overall yield was due to the difficulty in aromatization of initial adduct **17** to naphthoate ester **18**. If this second step in the synthesis of **18** could be improved, then **18** could become accessible enough to enable its use in these studies. Remarkably, when we applied Citterio's conditions to the aromatization of the cyclization product obtained from β-ketoester **24** (the corresponding methyl ester of **16**), we were delighted to find that aromatization occurred in a greatly improved yield of 93%. Using this new protocol, naphthoate

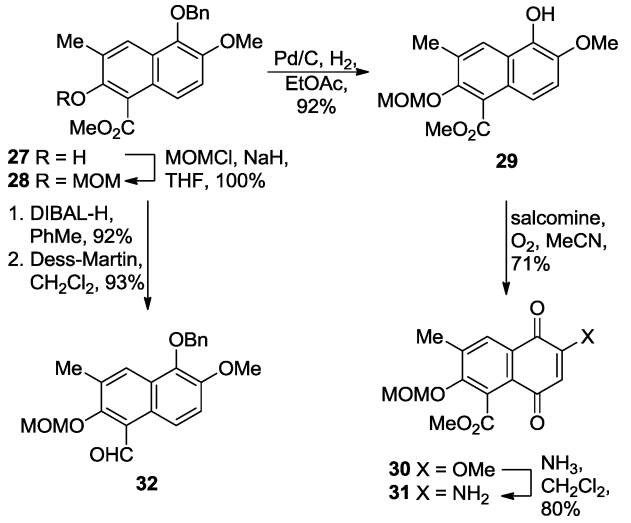
dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

ester **27** (the corresponding methyl ester of **18**) could now be prepared in 83% yield over two steps from β-ketoester **24** and is therefore a viable building block for use in total synthesis.

Reviewing the above results, we decided that although both β-ketoesters **20** and **24** underwent conversion into the corresponding naphthoates in similar yields, **24** would be a better choice with which to continue the synthesis. Although β-ketoester **20** might appear to be a more advanced and useful intermediate as it already contains a protected amino group, the much greater difficulty in preparing this material offset this advantage. Indeed, under the improved conditions described above, naphthoate **27** can now be prepared in 53% over six steps from inexpensive *o*-vanillin, whereas even after careful optimization, **25** can only be prepared in 14% over nine steps, a significant difference in number of steps and overall yield.

With large amounts of naphthoate **27** now available, manipulation of the ester and development of the latent quinone functionality was investigated. Thus, naphthol **27** was protected as the MOM ether **28** and, following debenzylation to naphthol **29**, oxidized to the corresponding naphthoquinone **30** using oxygen and a catalytic amount of the cobalt(II) salen complex salcomine (Scheme 5). Initially, this reaction appeared

Scheme 5. Conversion of 27 to Building Blocks for the Synthesis of Aminonaphthoquinones

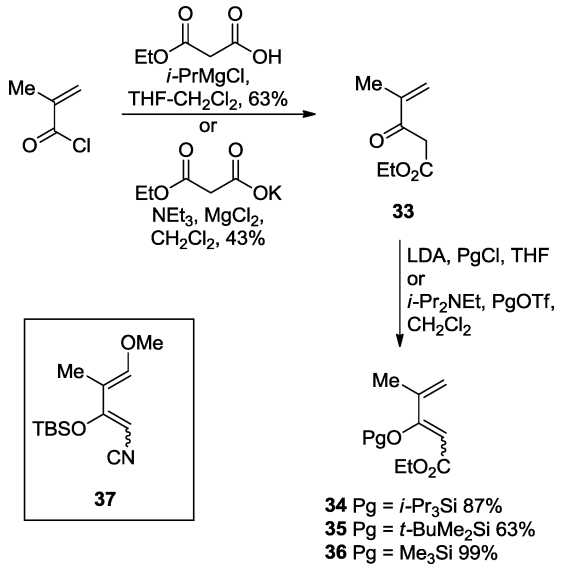


to be quite capricious, but upon further investigation it was discovered that the yield was highly dependent on the commercial source of the salcomine used. With the methoxynaphthoquinone **30** in hand, only displacement of the methoxy group with ammonia was required to complete the target naphthoquinone nucleus, and this was accomplished by treatment with liquid ammonia in a pressure vessel at −78 °C followed by warming to room temperature to give aminonaphthoquinone **31** in good yield. Unfortunately, further manipulation of the ester in this substrate was complicated by the presence of the sensitive aminonaphthoquinone ring system, indicating that introduction of the *ansa* chain might be easier on a naphthalene system instead of a naphthoquinone. Therefore, naphthoate ester **28** was also converted into the corresponding naphthaldehyde **32**, as it was anticipated that this might be a more useful precursor for the carbon−carbon bond-forming reactions required to introduce the *ansa* chain.

Thus, two useful naphthalene building blocks **31** and **32** for the synthesis of the ansamycin antiobiotics were now available in eight and nine steps, respectively. However, although this route was both straightforward and scalable, it did have the disadvantage of being quite linear, lengthy, and inflexible if a range of different aminonaphthoquinones needed to be rapidly prepared.

Given our interest in the Diels−Alder reaction of aminobenzoquinones for the preparation of building blocks for the synthesis of aminonaphthoquinone-containing natural products,[22,30] we speculated that a more direct approach to this type of system would be possible. However, this would require the use of a Danishefsky-type diene bearing an ester, and at the outset of these studies, no diene in this class containing an electron withdrawing group had been reported. Fortunately, Nazarov-type ester **33** had already been described in the literature and provided a convenient starting point to launch an investigation into the synthesis of such dienes (Scheme 6).

Scheme 6. Preparation of Ethyl 3-Siloxypenta-2,4-dienoates 34−36

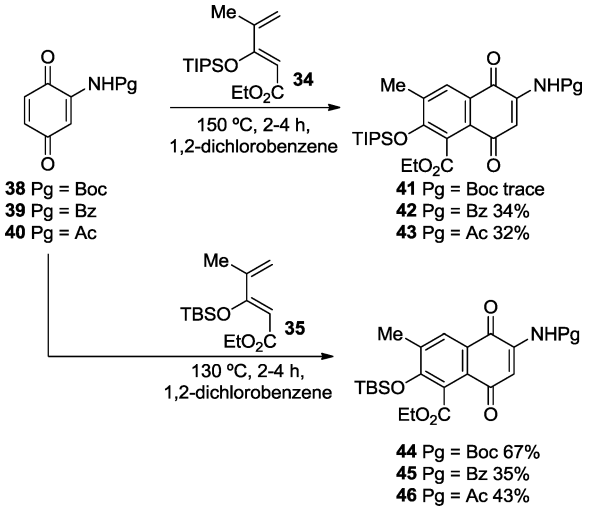


Initially, ester **33** was synthesized by reaction of the dianion of ethyl hydrogen malonate, formed using a slight excess of isopropylmagnesium chloride, with methacryloyl chloride, followed by decarboxylation.[31] However, upon scale-up of this route, the slightly lower yielding procedure of Miyata was employed,[32] as this was more convenient and practical. With ester **33** in hand, a range of three dienes bearing TMS, TBS, and TIPS groups, respectively, was prepared so that their reactivity could be compared. While this work was in progress, the related nitrile-containing diene **37** was reported by Trauner, prepared in four steps from methyl methacrylate.[33]

With a suitable range of dienes and protected aminobenzoquinones in hand, their union by Diels−Alder reaction was now investigated. Initially, TIPS-protected diene **34** was synthesized and trialed, as several synthetic steps would have to be carried out after the Diels−Alder reaction and a fairly robust protecting group would therefore be required. The results of reacting this diene with the previously described protected aminobenzoquinones **38**−**40** are shown below (Scheme 7). Because of the deactivating effect of the ester and the steric barrier to adopting the reactive S-*cis* conformation imposed by

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

Scheme 7. Initial Diels–Alder Reactions of Ethyl 3-Siloxypenta-2,4-dienoates with Aminobenzoquinones



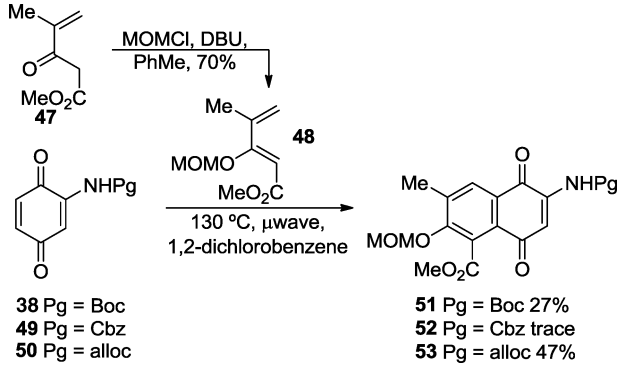
the TIPS group, diene **34** proved to be quite unreactive, and the Diels–Alder reaction therefore had to be carried out at elevated temperature. Thus, when diene **34** was heated with benzoquinones **39** and **40** to 150 °C in 1,2-dichlorobenzene, the expected naphthoquinone products **42** and **43** were obtained, albeit in low yield. The use of excess diene or quinone did not improve the yields obtained, and no other byproducts were isolated. Although the reaction was successful with benzoyl- and acetyl-protected aminobenzoquinones **39** and **40**, only traces of product were observed when Boc-protected aminobenzoquinone **38** was employed, possibly due to the known thermal instability of this protecting group.

Next, the corresponding TBS-protected diene **35** was studied and found to undergo the Diels–Alder reaction at a slightly lower temperature (130 °C), although the yields of the reaction remained moderate (Scheme 7). At this lower temperature, the Boc-protected aminobenzoquinone **38** could be used and was found to perform considerably better than the acetyl- and benzoyl-protected compounds, although this yield was not maintained upon scale-up. Thus, although the reaction gave the desired naphthoquinone in a reasonable 67% yield when conducted on 70 mg (0.3 mmol) scale, when the reaction was run on gram-scale (4.5 mmol) the yield decreased dramatically to 16%.

Finally, the TMS-protected diene **36**, readily synthesized by treatment of ester **33** with TMSCl and LDA, was found to be very unstable and difficult to even isolate and characterize. No Diels–Alder products were observed from reactions of this diene with the above dienophiles at ambient or elevated temperatures, and the unreacted benzoquinones **38**–**40** could be recovered from the reaction mixture.

Unfortunately, although 2D NMR experiments and previous studies on Diels–Alder reactions of this type appeared to support the regiochemical assignments made above,[22,34] unambiguous proof by X-ray crystallographic analysis was not possible due to the oily/amorphous nature of the naphthoquinone products. Therefore, it was decided to access the previously described napthoquinone **31** from the oxidative cyclization route described above (Scheme 5) using this Diels–Alder methodology in order to allow the regiochemistry of the Diels–Alder reaction to be confirmed. In order to minimize the number of steps required to achieve this, diene **48**, bearing a MOM-protecting group in place of the silyl protecting group previously employed, was synthesized (Scheme 8). As far as we

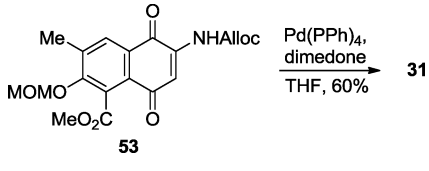
Scheme 8. Interception of a Previous Intermediate



are aware, this is only the second example of a MOM-protected Danishefsky-type diene synthesized to date,[35] and this protecting group appears to offer an excellent, more atom efficient alternative to the silyl protecting groups commonly employed in this role. The stability of MOM-protected diene **48** appears to be similar to that of the TBS protected diene **35** described above, and it could be purified by column chromatography and stored for several weeks after preparation. Again, a relatively high temperature (160 °C) was required for the Diels–Alder reaction with Boc-protected aminobenzoquinone **38**, and the yield obtained was somewhat lower than that obtained for TBS-protected diene **35**. However, despite this success, it was clear that removal of the Boc-protecting group in **51** would not be possible without disturbing the more sensitive MOM ether. Thus, two new aminobenzoquinones bearing alloc and Cbz protecting groups (**49** and **50** respectively; see the Experimental Section for details) were prepared in the hope that these groups would prove to be orthogonal to the MOM ether. Although the Cbz-protected aminobenzoquinone **49** only gave traces of the desired aminonaphthoquinone product **52** in the Diels–Alder reaction, accompanied by extensive degradation of both starting materials, the alloc-protected quinone **50** fared better, giving naphthoquinone **53** in 47% yield.

Cleavage of the allyloxycarbamate to reveal the amino-naphthoquinone **31** without affecting the sensitive MOM ether was carried out by stirring with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and excess dimedone at room temperature in THF (Scheme 9). Comparison of spectroscopic data for material prepared via this Diels–Alder route with that recorded for **31** prepared by the unambiguous route above (Scheme 5) allowed us to conclude that we had been correct in our assignment of the structures of the Diels–Alder adducts. Furthermore, we have demonstrated that the use of an alloc-protected aminobenzoquinone **50** in the Diels–

Scheme 9. Deprotection of Naphthoquinone 54 and Completion of 31 by Diels–Alder Route



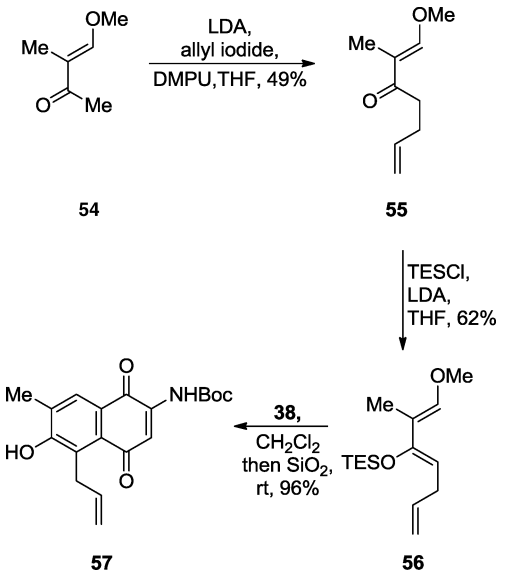
dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

Alder reaction is useful in the preparation of aminonaphthoquinone systems where the amine must be unmasked without disturbing acid and base sensitive functional groups, and the use of such orthogonally protected naphthoquinones could find future use in natural products synthesis.

With esters such as **44**–**46** now in hand, attempts were made to convert the ester into the corresponding aldehyde, as this would provide a more suitable handle for attachment of the *ansa* chain. Although the presence of the naphthoquinone moiety precluded reduction directly to the aldehyde, it was hoped that the use of excess reducing agent (e.g., lithium borohydride or lithium aluminum hydride) would allow reduction of the quinone and the ester. It was anticipated that the hydroquinone would reoxidize rapidly upon workup and then a simple oxidation of the benzylic alcohol would be required to obtain the desired aldehyde. Unfortunately, manipulation of the ester could not be carried out without a separate step to reduce and protect the quinone. In addition, amide formation at aminonaphthoquinones has been shown to be challenging due to the comparatively low reactivity of the amino group stemming from delocalization of the nitrogen lone pair into the quinone system. Hence, temporary reduction of the aminonaphthoquinone to facilitate coupling at this position is a common sight in the total synthesis of natural products containing this core, and thus, performing this step early, to enable manipulation of the ester, would likely not lengthen the overall synthetic sequence.

From these initial studies it became apparent that the inclusion of an electron-withdrawing group in Danishefsky-type dienes has a deleterious effect on their reactivity and restricts their use in synthesis due to the low yields and poor scalability of the reactions. All efforts to include an additional activating group such as the second alkoxy group in Trauner's diene **37** were met with failure, and so a different approach was taken. A number of alternative dienes were considered, containing a latent carbonyl group in place of the esters used above, and a new diene **56**, containing an allyl group, was synthesized (Scheme 10). The route began from known ester **54**, readily prepared in a two-step one-pot transformation from butanone, and the required allyl group was introduced by alkylation with LDA and allyl iodide in the presence of DMPU. Treatment of the allylated product with LDA and TESCl as before gave triene **56** whose reactivity in the Diels–Alder reaction was then investigated. Gratifyingly, **56** was far more reactive than the dienes described above, undergoing a Diels–Alder reaction with aminobenzoquinone **38** at room temperature in just 2 h. Aromatization by stirring with silica gel was also rapid, and aminonaphthoquinone **57** was obtained in almost quantitative yield. Unfortunately, the major product from the Diels–Alder reaction lacked the TES protecting group, which was invariably lost during the aromatization step. Surprisingly, when the corresponding TBS protected diene was prepared and subjected to the Diels–Alder reaction, the unprotected naphthol **57** was again the major product. Despite the loss of the protecting group during aromatization, an efficient route to allylnaphthoquinone **57** had been developed which could easily be used to produce gram-quantities of this material, and methods were then investigated for functionalization of the allyl chain.

Scheme 10. Diels–Alder Reaction of Triene 56



Unexpectedly, isomerization of the allyl group to the corresponding prop-1-enyl group proved challenging under a range of ruthenium- and rhodium-mediated conditions. A possible reason for the failure of these methods could be the presence of the quinone in **57**, which may serve to intercept the metal hydride intermediates through which such transformations are believed to proceed.[36] Indeed, the addition of a small amount of benzoquinone to metathesis reactions using Grubbs' ruthenium-based catalysts is a well-known tactic to avoid unwanted isomerization.[37] After some experimentation, it was found that bis(acetonitrile)dichloropalladium(II) in boiling dichloromethane did effect isomerization to the desired naphthoquinone **58**, although the yield was modest (Scheme 11). To our surprise, isomerization on protected derivatives of **57** under these conditions failed completely. Oxidative cleavage using both ozone and Lemieux–Johnson-type conditions on **58** was unsuccessful, and reaction mixtures subjected to these conditions rapidly decolorized, suggesting that oxidation was instead occurring at the quinone olefin.

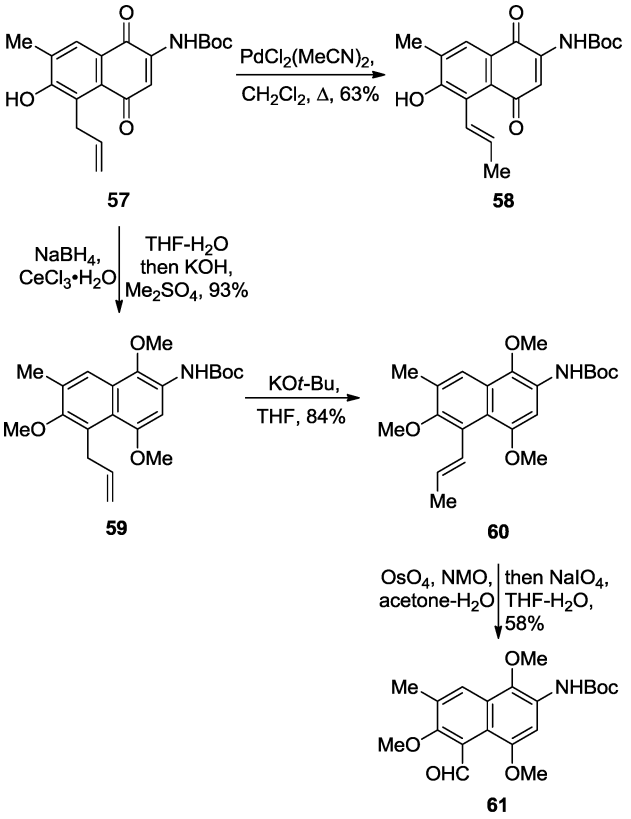
In light of these difficulties, it was finally decided that in order to manipulate the allyl group and thus connect the *ansa* chain reduction of the quinone would be required. Thus, allylnaphthoquinone **57** was reduced and trimethylated by exposure to Luche conditions, followed by treatment with potassium hydroxide and dimethyl sulfate to give naphthalene **59** in excellent yield.[33] Surprisingly, the isomerization step remained challenging, as allyl naphthalene **59** was now completely unreactive toward the palladium-based conditions described above, presumably due to the decreased acidity of the benzylic protons. However, it was found that isomerization of **59** to **60** could be carried out in excellent yield by simply heating with four equivalents of potassium *tert*-butoxide in THF. The use of fewer equivalents resulted in poor conversion and inseparable mixtures of product and starting materials. Ozonolysis of **60** resulted in a complex mixture of aldehydes that was difficult to purify, but a two-step protocol consisting of Upjohn dihydroxylation followed by oxidative cleavage of the resulting crude diol with sodium periodate did provide the desired aldehyde **61** in reasonable yield.

■ CONCLUSION

In conclusion, two routes suitable for the preparation of building blocks applicable to the synthesis of the aminonaphthoquinone antibiotics have been described. The first,

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

Scheme 11. Isomerization of Allylnaphthoquinone 57

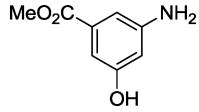


based on the oxidative radical cyclization methodology developed by Rickards, is highly scalable and allows for manipulation of the naphthoate ester (to introduce the *ansa* chain) before oxidation to the quinone has been carried out, obviating the need for a reduction and protection sequence later on. Second, a number of Diels–Alder approaches were investigated, leading to the development of a more concise route to a naphthaldehyde precursor, ready for the attachment of the *ansa* chain. Additionally, the synthesis of two new aminobenzoquinone dienophiles, bearing Cbz and alloc protecting groups, and their use in Diels–Alder reactions was described. The ability to remove these amine protecting groups under mild and specific conditions without unmasking other functionality in the rest of the molecule may prove useful in the syntheses of these compounds.

EXPERIMENTAL SECTION

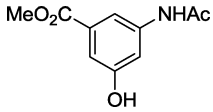
Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied unless otherwise stated. Tetrahydrofuran was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Toluene was dried by passage through activated alumina. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin-layer chromatography was carried out on aluminum-backed plates coated with silica gel and visualized under UV light at 254 and/or 360 nm and/or potassium permanganate or ethanolic vanillin dip. Chromatography was carried out on silica gel. Fully characterized compounds were chromatographically homogeneous. Infrared spectra were recorded in the range 4000–600 cm^{-1} as solutions in chloroform, as Nujol mulls, or as a solid in attenuated total reflectance (ATR) mode. NMR spectra were recorded at the frequencies stated. Chemical shifts are quoted in ppm and J values in hertz. Chemical shift values are referenced against residual proton in the deuterated solvents. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 are assigned from DEPT spectra; all others are quaternary C. High-resolution mass spectra were recorded on an ESI time-of-flight spectrometer with electrospray ionization.

Methyl 3-Amino-5-hydroxybenzoate.



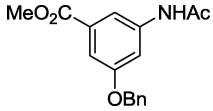
3,5-Dihydroxybenzoic acid (6.0 g, 39.0 mmol), ammonium chloride (5.1 g, 97.0 mmol), and aqueous ammonia solution (28%; 18.0 mL) were heated in a steel bomb at 180 °C for 40 h. The reaction mixture was allowed to cool to rt, taken up in methanol, and evaporated to dryness. The dry residue was then taken up in methanol (300 mL), treated dropwise with concentrated sulfuric acid (9.0 mL), and heated at reflux for 36 h. The reaction mixture was cooled to rt and concentrated, and the residue taken up in cold water (150 mL). The aqueous phase was then extracted with ether (3 × 100 mL), and the combined organic layers were washed with sulfuric acid (1 M; 200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated to give the byproduct methyl 3,5-dihydroxybenzoate. The acidic aqueous washings were combined, adjusted to pH 7 by addition of solid $NaHCO_3$, and then extracted with ethyl acetate (6 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual red oil was purified by flash column chromatography on silica gel, eluting with ethyl acetate–dichloromethane (1:4–2:3) to give the title compound as a pale yellow oil that crystallized on standing (3.81 g, 59%): mp 123–125 °C (lit.[38] mp 125–127 °C); HRMS found [M–H^+] 166.0509, $C_8H_8NO_3^-$ requires 166.0499; IR ν_{max} (ATR)/cm^{-1} 3402, 3319, 1706, 1600, 1362, 1346, 1302, 1253, 1183, 1004, 766; NMR δ_H (400 MHz; CD_3OD) 6.89 (1H, t, J 2.0), 6.79 (1H, t, J 2.0), 6.41 (1H, t, J 2.0), 3.84 (3H, s); NMR δ_C (100 MHz; CD_3OD) 169.2 (C), 159.4 (C), 150.5 (C), 132.9 (C), 109.2 (CH), 107.8 (CH), 107.1 (CH), 52.5 (Me). Data were consistent with those found in the literature.[38]

Methyl 3-Acetylamino-5-hydroxybenzoate.



Acetic anhydride (1.41 mL, 15.0 mmol) was added dropwise to methyl 3-amino-5-hydroxybenzoate (2.50 g, 15.0 mmol) in dry pyridine (6.0 mL) at 0 °C. The reaction mixture was warmed to rt and poured into hydrochloric acid (1 M; 50 mL). The layers were separated, the aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant cream solid was heated in ethyl acetate (50 mL) and methanol (10 mL), and the solution was cooled and filtered to give the title compound as a colorless powder (2.936 g, 76%): mp 227–229 °C (lit.[39] mp 230–232 °C); HRMS found [M–H^+] 208.0611, $C_{10}H_{10}NO_4^-$ requires 208.0604; IR ν_{max} (ATR)/cm^{-1} 3364, 3112, 1712, 1653, 1599, 1478, 1433, 1320, 1244, 1020, 873, 766; NMR δ_H (400 MHz; CD_3OD) 8.27 (1H, s), 8.07 (1H, s), 7.81 (1H, s), 4.53 (3H, s), 2.77 (3H, s); NMR δ_C (100 MHz; CD_3OD) 171.8 (C), 168.3 (C), 159.2 (C), 141.3 (C), 132.7 (C), 113.2 (CH), 112.8 (CH), 112.7 (CH), 52.7 (Me), 23.9 (Me). The data obtained matched those previously reported.[39]

Methyl 3-Acetylamino-5-benzyloxybenzoate.

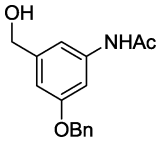


Benzyl bromide (301 μL, 2.53 mmol) was added to methyl 3-acetylamino-5-hydroxybenzoate (530 mg, 2.53 mmol) and K_2CO_3 (699 mg, 5.06 mmol) in acetone (50 mL), and the reaction mixture

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

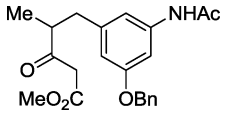
was heated to reflux and stirred for 16 h. The resulting solution was cooled to rt and concentrated, and the residue was taken up in water (30 mL) and ethyl acetate (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with water (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−dichloromethane (1:4), to give the title compound as a colorless oil that solidified on standing (614 mg, 81%): mp 121−123 °C; HRMS found [M + H^+] 300.1226, $C_{17}H_{18}NO_4^+$ requires 300.1230; IR ν_{max} (ATR)/cm^{-1} 3272, 2997, 1714, 1652, 1531, 1348, 1304, 1232, 1171, 764; NMR δ_H (400 MHz; $CDCl_3$) 7.75 (1H, s), 7.57 (1H, s), 7.43−7.32 (6H, m), 5.06 (2H, s), 3.88 (3H, s), 2.16 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 169.2 (C), 166.9 (C), 159.2 (C), 139.5 (C), 136.4 (C), 131.4 (C), 128.6 (CH), 128.1 (CH), 127.6 (CH), 113.3 (CH), 111.3 (CH), 111.1 (CH), 70.2 (CH_2), 52.3 (Me), 24.3 (Me).

3-Benzyloxy-5-hydroxymethylacetanilide.



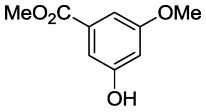
Lithium aluminum hydride (38 mg, 1.00 mmol) in THF (1.0 mL) was added to methyl 3-acetylamino-5-benzyloxybenzoate (300 mg, 1.00 mmol) in THF (2.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, warmed to rt, diluted with THF (10 mL), and quenched by careful addition of water (0.3 mL). The reaction mixture was filtered through a pad of Celite, washing with ethyl acetate (3 × 30 mL). The filtrate was concentrated in vacuo to give the title compound as a colorless oil that solidified on standing and did not require further purification (269 mg, 99%): mp 146−147 °C; HRMS found [M + H^+], 272.1282, $C_{16}H_{18}NO_3^+$ requires 272.1281; IR ν_{max} (ATR)/cm^{-1} 3298, 3116, 2858, 1665, 1612, 1564, 1438, 1283, 1164, 1031, 741; NMR δ_H (400 MHz; CD_3OD) 7.45−7.44 (2H, m), 7.40−7.38 (2H, m), 7.33−7.29 (1H, m), 7.27 (1H, t, *J* 2.0), 7.10 (1H, s), 6.78 (1H, s), 5.08 (2H, s), 4.56 (2H, s), 2.12 (3H, s); NMR δ_C (100 MHz; CD_3OD) 171.7 (C), 160.7 (C), 144.8 (C), 141.0 (C), 138.7 (C), 129.5 (CH), 128.9 (CH), 128.6 (CH), 112.0 (CH), 110.0 (CH), 106.8 (CH), 71.0 (CH_2), 65.0 (CH_2), 23.9 (Me).

Methyl 5-(3-Acetylamino-5-benzyloxy-phenyl)-4-methyl-3-oxopentanoate (20).



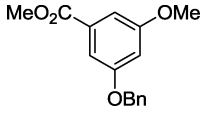
Phosphorus tribromide (77 μL, 0.82 mmol) was added dropwise to a stirred solution of 3-benzyloxy-5-hydroxymethylacetanilide (200 mg, 0.74 mmol) in dry 1,4-dioxane (2.5 mL) at 40 °C. The reaction mixture was stirred at 40 °C for 1 h, cooled to rt, and poured into saturated aqueous sodium hydrogen carbonate solution (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−dichloromethane (1:19) to give 3-benzyloxy-5-bromomethylacetanilide (**19**) as a pale yellow foam (188 mg, 76%) that was used directly without full characterization: HRMS found [M + H^+], 334.0430, $C_{16}H_{17}{}^{79}BrNO_2^+$ requires 334.0437); NMR δ_H (400 MHz; $CDCl_3$) 7.46−7.43 (6H, m), 7.20 (1H, br s), 7.10 (1H, s), 6.79 (1H, s), 5.08 (2H, s), 4.43 (2H, s), 2.19 (3H, s). 3-Benzyloxy-5-bromomethylacetanilide (**19**) (156 mg, 0.47 mmol) in THF (2 mL) was treated with sodium hydride (19 mg, 0.47 mmol) at 0 °C, stirred for 10 min at this temperature, and then added via cannula to a freshly prepared solution of the dianion of methyl 3-oxopentanoate at 0 °C. [The dianion was prepared by the dropwise addition of methyl 3-oxopentanoate (83 μL, 0.66 mmol) to a suspension of sodium hydride (26 mg, 0.66 mmol) in THF (1.5 mL) at 0 °C. The resulting solution was warmed to rt, stirred for 10 min, and then recooled to 0 °C. *n*-Butyllithium (2.5 M solution in hexanes; 264 μL, 0.66 mmol) was added over 15 min, and the yellow solution was stirred at 0 °C for 45 min before use.] The reaction mixture was warmed to rt over 1.5 h and quenched with aqueous NaH_2PO_4 solution (20%; 10 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous ammonium chloride solution (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−dichloromethane (1:4) to give the title compound as a colorless oil (112 mg, 62%): HRMS found [M + H^+] 384.1805, $C_{22}H_{26}NO_5^+$ requires 384.1806; IR ν_{max} ($CHCl_3$)/cm^{-1} 3436, 2929, 1746, 1713, 1616, 1594, 1456, 1313, 1155, 1060, 868; NMR δ_H (400 MHz; $CDCl_3$) 7.46−7.32 (5H, m), 7.19 (1H, s), 6.78 (1H, s), 6.55 (1H, s), 5.06 (2H, s), 3.71 (3H, s), 3.43 (1H, d, *J* 15.6), 3.37 (1H, d, *J* 15.6), 3.00−2.91 (2H, m), 2.59−2.52 (1H, m), 2.17 (3H, s), 1.13 (3H, d, *J* 6.4); NMR δ_C (100 MHz; $CDCl_3$) 168.3 (C), 167.9 (C), 159.4 (C), 141.1 (C), 139.1 (C), 138.2 (C), 136.7 (C), 128.6 (CH), 128.0 (CH), 127.6 (CH), 112.6 (CH), 111.8 (CH), 104.4 (CH), 70.0 (CH_2), 52.3 (Me), 48.4 (CH_2), 48.1 (CH), 38.9 (CH_2), 24.8 (Me), 16.3 (Me).

Methyl 3-Hydroxy-5-methoxybenzoate.



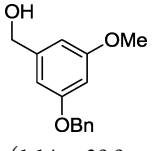
Iodomethane (1.86 mL, 30.0 mmol) were added to methyl 3,5-dihydroxybenzoate (5.04 g, 30.0 mmol) and K_2CO_3 (4.55 g, 33.0 mmol) in acetone (150 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 15 h, and filtered, washing with ethyl acetate (100 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:39−1:7) to give the title compound as a colorless crystalline solid (2.11 g, 39%): mp 94−96 °C (lit.[40] mp 93−95 °C); HRMS found M^+ 182.0575, $C_9H_{10}O_4^+$ requires 182.0574; IR ν_{max} ($CHCl_3$)/cm^{-1} 3593, 2952, 1720, 1602, 1493, 1456, 1347, 1323, 1277, 1147, 1104, 1057, 1005; NMR δ_H (400 MHz; $CDCl_3$) 7.22 (1H, d, *J* 1.2), 7.16 (1H, dd, *J* 2.1, 1.2), 6.66 (1H, t, *J* 2.1), 3.93 (3H, s), 3.82 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 167.1 (C), 160.9 (C), 156.9 (C), 132.0 (C), 109.3 (CH), 107.1 (CH), 106.7 (CH), 55.6 (Me), 52.4 (Me). The data obtained matched those found in the literature.[40]

Methyl 3-Benzyloxy-5-methoxybenzoate.



Benzyl bromide (3.75 mL, 31.5 mmol) was added to methyl 3-hydroxy-5-methoxybenzoate (5.74 g, 31.5 mmol) and K_2CO_3 (8.71 g, 63.0 mmol) in acetone (500 mL). The reaction mixture was heated to reflux, stirred for 12 h, cooled, and filtered, washing with ethyl acetate (100 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:7) to give the title compound as a colorless oil (8.50 g, 99%): HRMS found [M + H^+] 273.1137, $C_{16}H_{17}O_4^+$ requires 273.1121; IR ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1718, 1597, 1456, 1439, 1380, 1350, 1325, 1303, 1156, 1106, 1061; NMR δ_H (400 MHz; $CDCl_3$) 7.48−7.36 (5H, m), 7.33 (1H, dd, *J* 2.0, 1.2), 7.25 (1H, dd, *J* 2.0, 1.2), 6.76 (1H, t, *J* 2.4), 5.10 (2H, s), 3.93 (3H, s), 3.83 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 166.8 (C), 160.7 (C), 159.8 (C), 136.6 (C), 132.1 (C), 128.7 (CH), 128.1 (CH), 127.6 (CH), 108.0 (CH), 107.5 (CH), 106.5 (CH), 70.3 (CH_2), 55.6 (Me), 52.3 (Me).

3-Benzyloxy-5-methoxybenzyl Alcohol.

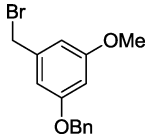


Lithium aluminum hydride (1.14 g, 30.0 mmol) in THF (40 mL) was added to methyl 3-benzyloxy-5-methoxybenzoate (8.17 g, 30.0 mmol) in THF (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and rt for 1 h and then diluted with THF (50 mL). Water (2.0

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

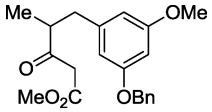
mL) was carefully added, and the colorless suspension was stirred for 10 min and then filtered through Celite, washing with ethyl acetate (2 × 150 mL). The filtrate was concentrated to give the title compound as a colorless oil that did not require further purification (7.0 g, 96%): HRMS found [M + Na^+] 267.0999, $C_{15}H_{16}NaO_3^+$ requires 267.0992; IR ν_{max} ($CHCl_3$)/cm^{-1} 3607, 2941, 1597, 1456, 1381, 1349, 1321, 1296, 1156, 1066; NMR δ_H (400 MHz; $CDCl_3$) 7.46−7.35 (5H, m), 6.63 (1H, s), 6.56 (1H, s), 6.50 (1H, t, *J* 2.2), 5.06 (2H, s), 4.64 (2H, d, *J* 5.2), 3.80 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 161.0 (C), 160.2 (C), 143.5 (C), 136.9 (C), 128.6 (CH), 128.0 (CH), 127.6 (CH), 105.4 (CH), 104.9 (CH), 100.5 (CH), 70.1 (CH_2), 65.3 (CH_2), 55.4 (Me). Data obtained matched those previously reported.[28]

3-Benzyloxy-5-methoxybenzyl Bromide (21).



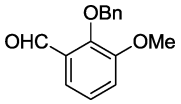
Phosphorus tribromide (1.28 mL, 13.6 mmol) was added to 3-benzyloxy-5-methoxybenzyl alcohol (3.0 g, 12.3 mmol) in 1,4-dioxane (30 mL), and the resulting solution was stirred at 40 °C for 1 h, cooled to rt, and poured into saturated aqueous sodium hydrogen carbonate solution (100 mL). Solid $NaHCO_3$ was added until the mixture was neutralized, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the title compound as a colorless oil that solidified on standing and did not require further purification (3.04 g, 81%): mp 52−53 °C; HRMS found M^+ 306.0255, $C_{15}H_{15}{}^{79}BrO_2^+$ requires 306.0250; IR ν_{max} ($CHCl_3$)/cm^{-1} 1597, 1456, 1381, 1348, 1324, 1297, 1155, 1062; NMR δ_H (400 MHz; $CDCl_3$) 7.47−7.37 (5H, m), 6.66 (1H, s), 6.59 (1H, s), 6.51 (1H, t, *J* 2.2), 5.07 (2H, s), 4.45 (2H, s), 3.81 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 160.9 (C), 160.1 (C), 139.8 (C), 136.7 (C), 128.4 (CH), 128.1 (CH), 127.6 (CH), 107.8 (CH), 107.4 (CH), 101.4 (CH), 70.2 (CH_2), 55.4 (Me), 33.6 (CH_2). ^1H and ^{13}C NMR data obtained matched those previously reported.[29]

Methyl 5-(3-Benzyloxy-5-methoxyphenyl)-4-methyl-3-oxopentanoate (22).



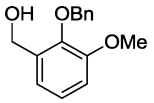
3-Benzyloxy-5-methoxybenzyl bromide (**21**) (1.45 g, 4.72 mmol) in THF (25 mL) was added via cannula to a freshly prepared solution of the dianion of methyl 3-oxopentanoate at 0 °C. [The dianion was prepared by the dropwise addition of methyl 3-oxopentanoate (830 μL, 6.61 mmol) to a suspension of sodium hydride (264 mg, 6.61 mmol) in THF (40 mL) at 0 °C. The resulting solution was warmed to rt, stirred for 10 min, and then recooled to 0 °C. *n*-Butyllithium (2.1 M solution in hexanes; 3.15 mL, 6.61 mmol) was added over 15 min, and the yellow solution was stirred at 0 °C for 45 min before use.] The reaction mixture was warmed to rt over 1.5 h and quenched with aqueous NaH_2PO_4 solution (20%; 6 mL). The aqueous phase was extracted with ethyl acetate (3 × 60 mL), and the combined organic extracts were washed with saturated aqueous ammonium chloride solution (150 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:19−1:9) to give the title compound as a colorless oil (1.35 g, 80%): HRMS found [M + Na^+] 379.1527, $C_{21}H_{24}NaO_5^+$ requires 379.1516; IR ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2876, 2842, 1746, 1714, 1652, 1608, 1595, 1456, 1378, 1348, 1316, 1149, 1065, 999; NMR δ_H (400 MHz; $CDCl_3$) 7.45−7.31 (5H, m), 6.43−6.41 (2H, m), 6.34 (1H, s), 5.04 (2H, s), 3.77 (3H, s), 3.70 (3H, s), 3.42 (1H, d, *J* 15.6), 3.37 (1H, d, *J* 15.6), 3.00 - 2.91 (2H, m), 2.61−2.51 (1H, m), 1.13 (3H, d, *J* 6.6); NMR δ_C (100 MHz; $CDCl_3$) 206.1 (C), 167.6 (C), 160.8 (C), 160.0 (C), 141.5 (C), 136.9 (C), 128.6 (CH), 128.0 (CH), 127.6 (CH), 107.7 (CH), 107.4 (CH), 99.3 (CH), 70.0 (CH_2), 55.3 (Me), 52.3 (Me), 48.4 (CH_2), 48.2 (CH), 39.2 (CH_2), 16.2 (Me).

2-Benzyloxy-3-methoxybenzaldehyde.



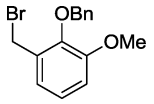
Potassium hydroxide pellets (3.98 g, 71.0 mmol) and benzyl chloride (8.17 mL, 71.0 mmol) were added to *o*-vanillin (10.0 g, 65.7 mmol) in ethanol (60 mL), and the reaction mixture was heated to reflux and stirred for 8 h. The resulting solution was cooled to rt, diluted with water (50 mL), and extracted with ether (3 × 75 mL). The combined ethereal extracts were washed with water (2 × 25 mL), aqueous sodium hydroxide solution (2 M; 5 × 50 mL), water (2 × 50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. The resulting orange oil was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:2) to give the title compound as a pale yellow crystalline solid (15.6 g, 98%): mp 45−47 °C (lit.[41] mp 45−46 °C); HRMS found [M + Na^+] 265.0836, $C_{15}H_{14}NaO_3^+$ requires 265.0841; IR ν_{max} ($CHCl_3$)/cm^{-1} 2841, 2363, 1690, 1585, 1482, 1456, 1371, 1268, 1070, 971, 914; NMR δ_H (400 MHz; $CDCl_3$) 10.26 (1H, s), 7.42−7.36 (6H, m), 7.22−7.16 (2H, m), 5.20 (2H, s), 3.97 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 190.3 (CH), 153.1 (C), 151.1 (C), 136.4 (C), 130.3 (C), 128.7 (CH), 128.6 (CH), 128.6 (CH), 124.3 (CH), 119.1 (CH), 118.0 (CH), 76.4 (CH_2), 56.1 (Me). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H 5.82. Found: C, 74.07; H, 5.81. The data obtained matched those previously reported.[41]

2-Benzyloxy-3-methoxybenzyl Alcohol.



Sodium borohydride (2.05 g, 54.1 mmol) was added portionwise to 2-benzyloxy-3-methoxybenzaldehyde (**19**) (12.5 g, 51.5 mmol) in methanol (250 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 1 h, diluted with water (10 mL), and concentrated in vacuo. The aqueous phase was extracted with ether (3 × 100 mL), and the combined ethereal extracts were dried ($MgSO_4$) and concentrated to give the title compound as a colorless crystalline solid that did not require further purification (12.9 g, 100%): mp 57−59 °C (lit.[42] mp 69−70 °C); HRMS found [M + Na^+] 267.1001, $C_{15}H_{16}NaO_3^+$ requires 267.0997; IR ν_{max} ($CHCl_3$)/cm^{-1} 3604, 2938, 1588, 1482, 1456, 1376, 1307, 1275, 1084, 1007; NMR δ_H (400 MHz; $CDCl_3$) 7.47−7.36 (5H, m), 7.09 (1H, t, *J* 8.0), 6.96−6.92 (2H, m), 5.11 (2H, s), 4.56 (2H, d, *J* 6.6), 3.94 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 152.5 (C), 145.6 (C), 137.5 (C), 135.0 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 124.3 (CH), 120.8 (CH), 112.2 (CH), 75.1 (CH_2), 61.7 (CH_2), 55.9 (Me). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.44; H, 6.47.

2-Benzyloxy-3-methoxybenzyl Bromide (23).

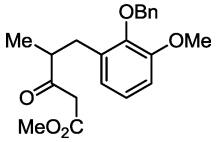


Phosphorus tribromide (1.85 mL, 19.7 mmol) was added to 2-benzyloxy-3-methoxybenzyl alcohol (**25**) (6.00 g, 24.6 mmol) in dioxane (60 mL), and the resulting solution was stirred at 40 °C for 1 h, cooled to rt, and poured into saturated aqueous sodium hydrogen carbonate solution (200 mL). The reaction mixture was neutralized with solid $NaHCO_3$, and the aqueous phase was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the title compound as a colorless oil that did not require further purification (6.98 g, 93%): IR ν_{max} ($CHCl_3$)/cm^{-1} 2940, 1587, 1483, 1462, 1376, 1312, 1274, 1083, 1071, 978; NMR δ_H (400 MHz; $CDCl_3$) 7.56−7.54 (2H, m), 7.44−7.34 (3H, m), 7.08 (1H, t, *J* 8.0), 7.00 (1H, dd, *J* 8.0, 1.6), 6.94 (1H, dd, *J* 8.0, 1.6), 5.18 (2H, s), 4.54 (2H, s), 3.92 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 152.9 (C), 146.2 (C), 137.6 (C), 132.2 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 124.3 (CH), 122.6 (CH), 113.0 (CH), 74.7 (CH_2), 55.9 (Me), 28.4 (CH_2). Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65;

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

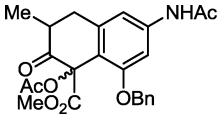
H, 4.92. Found: C, 59.00; H, 4.92. The data obtained matched those reported in the literature.[43]

Methyl 5-(2-Benzyloxy-3-methoxyphenyl)-4-methyl-3-oxopentanoate (24).



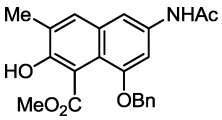
2-Benzyloxy-3-methoxybenzyl bromide (**23**) (8.2 g, 26.7 mmol) in THF (70 mL) was added via cannula to a freshly prepared solution of the dianion of methyl 3-oxopentanoate at 0 °C. [The dianion was prepared by the dropwise addition of methyl 3-oxopentanoate (4.69 mL, 37.4 mmol) to a suspension of sodium hydride (1.5 mg, 37.4 mmol) in THF (120 mL) at 0 °C. The resulting solution was warmed to rt, stirred for 10 min, and then recooled to 0 °C. *n*-Butyllithium (2.5 M solution in hexanes; 15.0 mL, 37.4 mmol) was added over 30 min, and the yellow solution was stirred at 0 °C for 45 min before use.] The reaction mixture was warmed to rt over 1.5 h and quenched with aqueous NaH_2PO_4 solution (20%; 60 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with saturated aqueous ammonium chloride solution (250 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:9−1:7) to give the title compound as a pale oil (8.2 g, 86%): HRMS found [M + Na^+] 379.1505, $C_{21}H_{24}NaO_5^+$ requires 379.1521; IR ν_{max} ($CHCl_3$)/cm^{-1} 2932, 1745, 1713, 1601, 1456, 1311, 1084, 998; NMR δ_H (400 MHz; $CDCl_3$) 7.50−7.46 (2H, m), 7.42−7.33 (3H, m), 7.00 (1H, dd, *J* 8.2, 7.6), 6.87 (1H, dd, *J* 8.2, 1.3), 6.72 (1H, dd, *J* 7.6, 1.3), 5.03 (1H, d, *J* 11.1), 5.08 (1H, d, *J* 11.1), 3.90 (3H, s), 3.67 (3H, s), 3.32 (1H, d, *J* 15.6), 3.26 (1H, d, *J* 15.6), 2.99−2.92 (2H, m), 2.53−2.47 (1H, m), 1.03 (3H, d, *J* 6.7); NMR δ_C (100 MHz; $CDCl_3$) 206.3 (C), 167.6 (C), 152.8 (C), 146.1 (C), 137.9 (C), 133.2 (C), 128.5 (CH), 128.2 (CH), 128.0 (CH), 123.9 (CH), 122.9 (CH), 122.8 (CH), 111.0 (CH), 74.8 (CH_2), 55.7 (Me), 52.2 (Me), 47.9 (CH_2), 47.0 (CH), 33.8 (CH_2), 15.8 (Me). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.96; H, 6.73.

Methyl 1-Acetoxy-6-acetylamino-8-benzyloxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate.



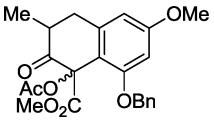
Methyl 5-(3-acetylamino-5-benzyloxy-phenyl)-4-methyl-3-oxopentanoate (**20**) (279 mg, 0.73 mmol) in dry, degassed acetic acid (6 mL) was added in one portion to anhydrous manganese(III) acetate (709 mg, 3.06 mmol). The reaction mixture was stirred at rt for 22 h, quenched with brine (15 mL), and concentrated to dryness in vacuo. The residue was taken up in water (40 mL), brine (40 mL), and chloroform (30 mL), and the aqueous phase was extracted with chloroform (4 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−dichloromethane (2:3) to give the title compound as a colorless oil (232 mg, 72%) as a 5:3 mixture of diastereomers: HRMS found [M + H^+] 440.1707, $C_{24}H_{26}NO_7^+$ requires 440.1704; NMR δ_H (400 MHz; $CDCl_3$) 7.67 (1H, br s, maj), 7.64 (1H, br s, min), 7.51−7.31 (6H, m), 6.78 (1H, s, maj), 6.71 (1H, s, min), 5.13 (1H, d, *J* 12.0), 5.03 (1H, d, *J* 12.0), 3.52 (3H, s, maj), 3.50 (3H, s, min), 3.44−3.23 (1H, m), 3.18−3.06 (1H, m), 2.96−2.78 (1H, m), 2.16 (3H, s), 2.07 (3H, s, maj), 2.07 (3H, s, min), 1.30−1.23 (3H, m).

Methyl 6-Acetylamino-8-benzyloxy-2-hydroxy-3-methylnaphthalene-1-carboxylate (25).



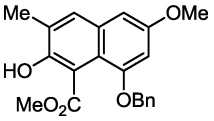
A suspension of methyl 1-acetoxy-6-acetylamino-8-benzyloxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (mixture of diastereomers from above; 108 mg, 0.25 mmol) and silica gel (1.0 g) in benzene (5 mL) was stirred at reflux for 1.5 h then at rt overnight. The reaction mixture was concentrated and the residue was purified by preparative TLC eluting with ethyl acetate−dichloromethane (2:3) to give the title compound as a colorless oil (41 mg, 43%): HRMS found [M − H^+] 378.1345, $C_{22}H_{20}NO_5^-$ requires 378.1347; IR ν_{max} ($CHCl_3$)/cm^{-1} 3688, 3037, 1683, 1601, 1415, 1242, 928; NMR δ_H (400 MHz; $CDCl_3$) 8.02 (1H, s), 7.75 (1H, s), 7.43−7.31 (5H, m), 7.21 (1H, s), 5.01 (2H, s), 3.37 (3H, s), 2.31 (3H, s), 2.16 (3H, s); NMR δ_C (100 MHz; CD_3OD) 172.6 (C), 171.7 (C), 154.4 (C), 151.8 (C), 137.5 (C), 136.0 (C), 131.2 (C), 131.6 (CH), 130.1 (CH), 129.8 (CH), 119.9 (C), 115.5 (C), 110.6 (CH), 102.3 (CH), 72.3 (CH_2), 52.5 (Me), 24.3 (Me), 17.4 (Me).

Methyl 1-Acetoxy-8-benzyloxy-6-methoxy-3-methyl-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylate.



Methyl 5-(3-benzyloxy-5-methoxy-phenyl)-4-methyl-3-oxopentanoate (**22**) (200 mg, 0.56 mmol) in dry, degassed acetic acid (4 mL) was added in one portion to anhydrous manganese(III) acetate (547 mg, 2.36 mmol). The reaction mixture was stirred at rt for 22 h, quenched with brine (3 mL), and concentrated to dryness in vacuo. The residue was taken up in water (50 mL), brine (50 mL), and chloroform (100 mL), and the aqueous phase was extracted with chloroform (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:7) to give the title compound as a colorless crystalline solid (91 mg, 40%) as a 3:2 mixture of diastereomers: mp 153−155 °C; HRMS found [M + Na^+] 435.1436, $C_{23}H_{24}NaO_7^+$ requires 435.1414; IR ν_{max} ($CHCl_3$)/cm^{-1} 1773, 1727, 1608, 1456, 1370, 1159, 1107, 1083, 1050; NMR δ_H (400 MHz; $CDCl_3$) 7.48−7.32 (5H, m), 6.43 (1H, dd, *J* 8.4, 1.8), 6.36 (1H, dd, *J* 5.1, 1.6), 5.14−5.00 (2H, m), 3.81 (3H, s), 3.55 (3H, s, maj), 3.52 (3H, s, min), 3.50−3.30 (1H, m), 3.23−3.07 (1H, m), 3.02−2.83 (1H, m), 2.11 (3H, s), 1.28 (3H, d, *J* 6.7, maj), 1.26 (3H, d, *J* 5.6, min); NMR δ_C (100 MHz; $CDCl_3$) 204.7 (C), 202.4 (C), 169.9, 169.3 (C), 167.6, 167.3 (C), 161.4, 161.1 (C), 158.2, 157.5 (C), 141.6 (C), 136.3, 136.2 (C), 128.5 (CH), 128.0 (CH), 127.0 (CH), 105.0, 104.0 (CH), 98.6, 98.4 (CH), 70.4, 70.2 (CH_2), 55.4 (Me), 53.2, 52.8 (Me), 43.1, 41.9 (CH), 38.8, 37.9 (CH_2), 20.8, 20.7 (Me), 15.7, 14.0 (Me).

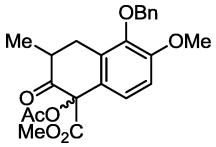
Methyl 8-Benzyloxy-2-hydroxy-6-methoxy-3-methylnaphthalene-1-carboxylate (26).



A suspension of methyl 1-acetoxy-8-benzyloxy-6-methoxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (mixture of diastereomers from above; 91 mg, 0.22 mmol) and silica gel (1.0 g) in benzene (5 mL) was stirred at reflux for 1.5 h then at rt overnight. The solvent was removed by concentration in vacuo, and the residue was purified by flash chromatography, eluted with ethyl acetate−light petroleum (1:2). The title compound was isolated as a colorless oily solid (15 mg, 19%): HRMS found [M + Na^+] 375.0878, $C_{21}H_{20}NaO_5^+$ requires 375.1208; IR ν_{max} (Nujol)/cm^{-1} 2954, 1677, 1611, 1515, 1438, 1398, 1269, 1161, 1096, 1023; NMR δ_H (400 MHz; $CDCl_3$) 7.96 (1H, s), 7.55 (1H, s), 7.45−7.37 (5H, m), 6.69 (1H, d, *J* 2.4), 6.65 (1H, d, *J* 2.4), 5.12 (2H, s), 3.90 (3H, s), 3.44 (3H, s), 2.40 (3H, d, *J* 0.8); NMR δ_C (100 MHz; $CDCl_3$) 171.6 (C), 156.9 (C), 154.2 (C), 153.0 (C), 136.4 (C), 131.5 (CH), 130.4 (C), 128.6 (CH), 128.2 (CH), 128.0 (C), 127.8 (CH), 117.0 (C), 108.7 (C), 100.3 (CH), 98.8 (CH), 70.9 (CH_2), 55.4 (Me), 52.0 (Me), 16.6 (Me).

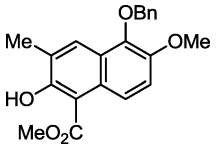
dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

Methyl 1-Acetoxy-5-benzyloxy-6-methoxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate.



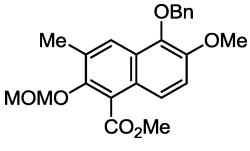
Methyl 5-(2-benzyloxy-3-methoxyphenyl)-4-methyl-3-oxopentanoate (**24**) (5.0 g, 14.0 mmol) in dry, degassed acetic acid (100 mL) was added in one portion to anhydrous manganese(III) acetate (13.7 g, 59.0 mmol) under an atmosphere of argon. The reaction mixture was stirred at rt for 22 h, quenched with brine (100 mL), and concentrated to dryness in vacuo. The residue was taken up in water (250 mL), brine (250 mL), and chloroform (500 mL), and then the aqueous phase was extracted with chloroform (4 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:7), to give the title compound as a colorless oil (5.35 g, 93%) as a 5:4 mixture of diastereomers: HRMS found [M + Na^+] 435.1017, $C_{23}H_{24}NaO_7^+$ requires 435.1420; IR ν_{max} ($CHCl_3$)/cm^{-1} 2958, 1738, 1602, 1490, 1456, 1372, 1283, 1082, 1044, 908; NMR δ_H (400 MHz; $CDCl_3$) 7.47–7.33 (5H, m), 7.19 (1H, dd, *J* 8.8, 2.0), 6.90 (1H, t, *J* 8.4), 5.09 (1H, d, *J* 11.3, maj), 5.05 (1H, d, *J* 11.1, min), 5.03 (1H, d, *J* 11.3, maj), 4.98 (1H, d, *J* 11.1, min), 3.93 (3H, s, maj), 3.90 (3H, s, min), 3.75 (3H, s, min), 3.65 (3H, s, maj), 3.41–3.28 (1H, m), 3.18–2.75 (1H, m), 2.59–2.45 (1H, m), 2.22 (3H, s, maj), 2.12 (3H, s, min), 1.24 (3H, d, *J* 6.1, maj), 1.22 (3H, d, *J* 6.1, min); NMR δ_C (100 MHz; $CDCl_3$) 205.6 (C), 202.6 (C), 169.0 (C), 167.3 (C), 153.0 (C), 144.0 (C), 137.2 (C), 132.6 (C), 128.8 (CH), 128.3 (CH), 128.1 (CH), 127.2 (C), 123.1 (CH), 111.2 (CH), 74.9 (CH_2), 55.8 (Me), 53.1 (Me), 42.6 (CH), 31.1 (CH), 20.9 (Me), 15.2 (Me).

Methyl 5-Benzyloxy-2-hydroxy-6-methoxy-3-methylnaphthalene-1-carboxylate (27).



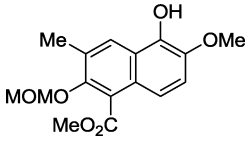
A suspension of methyl 1-acetoxy-5-benzyloxy-6-methoxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (mixture of diastereomers from above; 5.35 g, 13.0 mmol) and silica gel (54 g) in benzene (400 mL) was heated at reflux for 48 h and then allowed to cool to rt. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:7) to give the title compound as a very pale yellow oil that crystallized on standing (4.07 g, 89%): mp 81–83 °C; HRMS found [M + H^+], 353.1369. $C_{21}H_{21}O_5^+$ requires 353.1384; IR ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2957, 1650, 1429, 1320, 1281, 1244, 1112, 1020, 997, 909; NMR δ_H (400 MHz; $CDCl_3$) 8.46 (1H, dd, *J* 9.4, 0.8), 8.11 (1H, d, *J* 0.8), 7.57–7.55 (1H, m), 7.55–7.53 (1H, m), 7.45–7.29 (4H, m), 5.16 (2H, s), 4.11 (3H, s), 4.00 (3H, s), 2.38 (3H, d, *J* 1.2); NMR δ_C (100 MHz; $CDCl_3$) 173.3 (C), 162.9 (C), 146.9 (C), 142.1 (C), 137.7 (C), 129.4 (CH), 128.5 (CH), 128.4 (C), 128.4 (CH), 128.1 (CH), 126.1 (C), 124.4 (C), 121.5 (CH), 115.7 (CH), 103.8 (C), 75.6 (CH_2), 56.8 (Me), 52.4 (Me), 17.0 (Me). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.58; H, 5.67.

Methyl 5-Benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carboxylate (28).



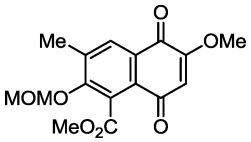
Methyl 5-benzyloxy-2-hydroxy-6-methoxy-3-methylnaphthalene-1-carboxylate (**27**) (1.00 g, 2.84 mmol) in THF (4 mL) was added to a suspension of sodium hydride (125 mg, 3.12 mmol) in THF (16 mL) at 0 °C. After 10 min, chloromethyl methyl ether (431 μL, 5.68 mmol) was added, and the solution was allowed to warm to rt. After 1 h, the reaction mixture was diluted with water (10 mL) and then extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9) to give the title compound as a colorless oil (1.13 g, 100%): HRMS found [M + H^+] 397.1641, $C_{23}H_{25}O_6^+$ requires 397.1646; IR ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2954, 2842, 1725, 1625, 1603, 1573, 1507, 1456, 1427, 1366, 1324, 1255, 1160; NMR δ_H (400 MHz; $CDCl_3$) 8.01 (1H, *J* 0.8), 7.57–7.54 (3H, m), 7.45–7.32 (4H, m), 5.17 (2H, s), 5.10 (2H, s), 4.06 (3H, s), 4.00 (3H, s), 3.61 (3H, s), 2.46 (3H, d, *J* 0.8); NMR δ_C (100 MHz; $CDCl_3$) 168.5 (C), 151.3 (C), 148.2 (C), 141.5 (C), 137.7 (C), 131.5 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 126.8 (C), 125.7 (C), 125.4 (CH), 123.3 (C), 120.7 (CH), 115.9 (CH), 100.4 (CH_2), 75.5 (CH_2), 57.5 (Me), 56.9 (Me), 52.5 (Me), 17.7 (Me).

Methyl 5-Hydroxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carboxylate (29).



A suspension of methyl 5-benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carboxylate (**28**) (499 mg, 1.26 mmol) and palladium-on-carbon (10 wt %; 13.0 mg, 0.13 mmol) in ethyl acetate (150 mL) was stirred under a hydrogen atmosphere at rt for 1.5 h. The reaction mixture was filtered through a pad of Celite, washing with ethyl acetate (200 mL), and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:7) to give the title compound as a pale yellow oil that crystallized on standing (355 mg, 92%): mp 121–122 °C; HRMS found [M + Na^+] 329.0992, $C_{16}H_{18}NaO_6^+$ requires 329.0996; IR ν_{max} ($CHCl_3$)/cm^{-1} 3538, 3009, 2954, 2843, 1726, 1638, 1605, 1579, 1512, 1444, 1386, 1349, 1287, 1251; NMR δ_H (400 MHz; $CDCl_3$) 8.08 (1H, t, *J* 0.9), 7.30 (1H, t, *J* 9.2), 7.22 (1H, t, *J* 9.2), 6.07 (1H, s), 5.10 (2H, s), 4.04 (3H, s), 3.97 (3H, s), 3.60 (3H, s), 2.50 (3H, d, *J* 0.9); NMR δ_C (100 MHz; $CDCl_3$) 168.5 (C), 151.3 (C), 141.1 (C), 139.3 (C), 130.7 (C), 125.7 (C), 124.9 (CH), 123.2 (C), 121.3 (C), 116.0 (CH), 113.8 (CH), 100.4 (CH_2), 57.5 (Me), 57.1 (Me), 52.4 (Me), 17.6 (Me).

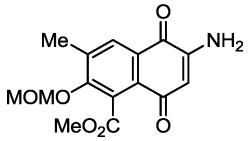
Methyl 5,8-Dihydro-6-methoxy-2-methoxymethoxy-3-methyl-5,8-dioxonaphthalene-1-carboxylate (30).



Oxygen was bubbled through a solution of methyl 5-hydroxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carboxylate (**29**) (50 mg, 0.16 mmol) and salcomine (Aldrich) (32 mg, 0.1 mmol) in acetonitrile (10 mL) for 15 min, and stirring was then continued under an atmosphere of oxygen for 15 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:7) to give the title compound as a pale yellow solid (37 mg, 71%): mp 134–136 °C; HRMS found [M + H^+] 321.0965, $C_{16}H_{17}O_7^+$ requires 321.0969; IR ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2954, 2846, 1735, 1684, 1654, 1616, 1578, 1458, 1364, 1316, 1251, 1160, 1104, 1029; NMR δ_H (400 MHz; $CDCl_3$) 8.04 (1H, d, *J* 0.4), 6.09 (1H, s), 5.10 (2H, s), 4.00 (3H, s), 3.89 (3H, s), 3.59 (3H, s), 2.46 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 183.4 (C), 178.9 (C), 167.6 (C), 160.1 (C), 158.0 (C), 138.8 (C), 131.0 (CH), 128.7 (C), 128.2 (C), 127.2 (C), 109.9 (CH), 100.8 (CH_2), 57.8 (Me), 56.5 (Me), 53.0 (Me), 17.4 (Me).

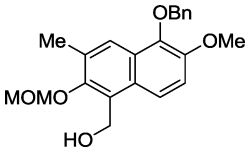
dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

Methyl 6-Amino-5,8-dihydro-2-methoxymethoxy-3-methyl-5,8-dioxonaphthalene-1-carboxylate (31).



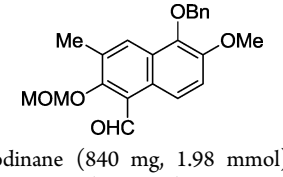
Ammonia was bubbled through a solution of methyl 5,8-dihydro-6-methoxy-2-methoxymethoxy-3-methyl-5,8-dioxonaphthalene-1-carboxylate (**30**) (21 mg, 0.07 mmol) in dichloromethane (1.5 mL) at −78 °C in a pressure tube. After 5 min, the pressure tube was sealed, and the solution was warmed to rt and stirred for 48 h. The sealed tube was carefully opened to release the pressure, and the reaction mixture was transferred to a round-bottomed flask with dichloromethane (20 mL), chloroform (10 mL), and ethyl acetate (20 mL) washings. The solvent was removed by concentration, and the residue was purified by flash column chromatography on silica gel eluted with ethyl acetate−light petroleum (2:5) to give the title compound as a bright orange solid (16 mg, 80%): mp 140−142 °C; HRMS found $[M + H^+]$, 306.0965. $C_{15}H_{16}NO_6^+$ requires 306.0972; IR ν_{max} $(CHCl_3)/cm^{-1}$ 3514, 3397, 3012, 1732, 1681, 1623, 1574, 1336, 1269, 1240, 1160, 909; NMR δ_H (400 MHz; $CDCl_3$) 7.97 (1H, d, *J* 0.8), 5.92 (1H, s), 5.26 (2H, br s), 5.11 (2H, s), 4.00 (3H, s), 3.61 (3H, s), 2.45 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 182.2 (C), 180.6 (C), 168.1 (C), 158.2 (C), 148.0 (C), 137.3 (C), 130.6 (CH), 130.2 (C), 128.3 (C), 126.7 (C), 104.9 (CH), 100.8 (CH_2), 57.8 (Me), 52.9 (Me), 17.3 (Me).

5-Benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalen-1-yl methanol.



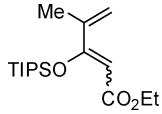
DIBAL-H (1 M solution in toluene; 2.36 mL, 2.36 mmol) was added over 20 min to methyl 5-benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carboxylate (**28**) (935 mg, 2.36 mmol) in toluene (40 mL) at −78 °C. After 1 h at this temperature, additional DIBAL-H (1 M solution in toluene; 3.54 mL, 3.54 mmol) was added over 30 min, and the resulting solution was stirred for 1 h and then warmed to rt. Methanol (5 mL) was added, and the solution was diluted with hydrochloric acid (1 M; 20 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), allowed to stand for 15 h,and then extracted again (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate−light petroleum (1:9−1:4) to give the title compound as an orange oil that crystallized on standing (793 mg, 92%): mp 76−78 °C; HRMS found $[M + Na^+]$, 391.1506. $C_{22}H_{24}NaO_5^+$ requires 391.1516; IR ν_{max} $(CHCl_3)/cm^{-1}$ 3489, 3011, 2939, 2909, 2842, 1603, 1508, 1431, 1365, 1274; NMR δ_H (400 MHz; $CDCl_3$) 7.98−7.96 (2H, m), 7.60−7.58 (2H, m), 7.46−7.35 (4H, m), 5.17 (2H, s), 5.07 (2H, d, *J* 5.2), 5.03 (2H, s), 4.01 (3H, s), 3.70 (3H, s), 3.02 (1H, s, br), 2.41 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 152.5 (C), 148.1 (C), 141.7 (C), 137.9 (C), 130.7 (C), 128.4 (CH), 128.3 (CH), 128.1 (C), 128.0 (CH), 127.8 (C), 127.4 (C), 123.8 (CH), 120.6 (CH), 115.3 (CH), 99.5 (CH_2), 75.4 (CH_2), 57.5 (Me), 56.9 (Me), 56.2 (CH_2), 17.9 (Me). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.81; H, 6.55.

5-Benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalene-1-carbaldehyde (32).



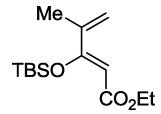
Dess−Martin periodinane (840 mg, 1.98 mmol) was added to 5-benzyloxy-6-methoxy-2-methoxymethoxy-3-methylnaphthalen-1-yl methanol (**28**) (611 mg, 1.66 mmol) in dichloromethane (40 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, rt for 1 h and then quenched with saturated aqueous sodium hydrogen carbonate solution (20 mL) and solid $Na_2S_2O_3$ (2.0 g). The reaction mixture was stirred vigorously for 10 min, the layers were separated, and the organic phase was washed with water (3 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:9−1:7) to give the title compound as a yellow crystalline solid (563 mg, 93%): mp 61−63 °C; HRMS found $[M + H^+]$, 367.1528. $C_{22}H_{23}O_5^+$ requires 367.1540; IR ν_{max} $(CHCl_3)/cm^{-1}$ 3443, 3011, 2939, 1677, 1597, 1567, 1504, 1464, 1435, 1357, 1275; NMR δ_H (400 MHz; $CDCl_3$) 10.73 (1H, s), 8.97 (1H, d, *J* 9.5), 8.22 (1H, s), 7.55−7.53 (2H, m), 7.44−7.35 (4H, m), 5.17 (2H, s), 5.14 (2H, s), 4.02 (3H, s), 3.64 (3H, s), 2.45 (3H, s); NMR δ_C (100 MHz; $CDCl_3$) 193.2 (CH), 161.4 (C), 148.6 (C), 141.1 (C), 137.6 (C), 130.9 (C), 130.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.1 (C), 125.5 (C), 122.8 (C), 121.7 (CH), 117.0 (CH), 101.5 (CH_2), 75.6 (CH_2), 58.1 (Me), 56.7 (Me), 17.4 (Me). Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 71.61; H, 6.01.

(*Z*)-Ethyl 4-Methyl-3-(triisopropylsiloxy)penta-2,4-dienoate (34).



Triisopropylsilyl trifluoromethanesulfonate (2.07 mL, 7.7 mmol) was added dropwise a solution of (*E*)-4-methoxy-3-methylbut-3-en-2-one[32] (1.0 g, 6.4 mmol) and Hünig's base (1.3 mL, 7.7 mmol) in dichloromethane (40 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 2 days, and then poured into saturated aqueous sodium hydrogen carbonate solution (50 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum (1:99) to give the title compound as a colorless oil (1.74 g, 87%; 1:2 inseparable mixture of diastereomers): HRMS found $[M + Na^+]$, 335.2011. $C_{17}H_{32}NaO_3Si^+$ requires 335.2013; IR ν_{max} $(CHCl_3)/cm^{-1}$ 2946, 2893, 2868, 1740, 1721, 1465, 1083, 1050, 884; NMR δ_H (300 MHz; $CDCl_3$; major) 5.61 (1H, br d, *J* 1.3), 5.34 (1H, s), 5.19 (1H, dq, *J* 1.3, 1.0), 4.14 (2H, q, *J* 7.2), 1.93 (3H, q, *J* 1.0), 1.40−1.22 (3H, m), 1.28 (3H, t, *J* 7.2), 1.11 (18H, d, *J* 7.3); NMR δ_H (300 MHz; $CDCl_3$; minor) 5.16 (1H, app. q, *J* 1.6), 5.14 (1H, s), 5.13 (1H, dq, *J* 1.6, 1.0), 4.11 (2H, q, *J* 7.2), 1.98 (3H, dd, *J* 1.6, 1.0), 1.40−1.22 (3H, m), 1.26 (3H, t, *J* 7.2) 1.12 (18H, *J* 6.8); NMR δ_C (75 MHz; $CDCl_3$; major) 170.1 (C), 164.0 (C), 141.5 (C), 118.4 (CH_2), 99.3 (CH), 59.3 (CH_2), 20.2 (CH), 18.0 (Me), 12.7 (Me); NMR δ_C (75 MHz; $CDCl_3$; minor) 170.1 (C), 164.0 (C), 141.5 (C), 116.7 (CH_2), 98.8 (CH), 59.5 (CH_2), 20.2 (CH), 17.9 (Me), 14.0 (Me).

(*Z*)-Ethyl 3-(*tert*-Butyldimethylsiloxy)-4-methylpenta-2,4-dienoate (35).

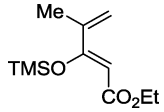


tert-Butyldimethylsilyl trifluoromethanesulfonate (0.88 mL, 3.84 mmol) was added to (*E*)-4-methoxy-3-methylbut-3-en-2-one[32] (500 mg, 3.20 mmol) and Hünig's base (0.67 mL, 3.84 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 1 h, and then poured into saturated aqueous sodium hydrogen carbonate solution (20 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a semisolid mixture. The solid was washed repeatedly with light petroleum, and the combined extracts were concentrated. The residual oil was purified by flash column chromatography on silica gel eluting with ethyl acetate−light petroleum to give the title compound as a colorless oil (545 mg, 63%): HRMS found $[M + H^+]$ 271.1719, $C_{14}H_{27}O_3Si^+$ requires 271.1724; IR ν_{max} $(CHCl_3)/cm^{-1}$ 2957, 2932,

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

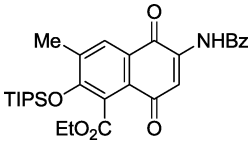
2898, 2859, 1712, 1599, 1256, 1177; NMR δ_H (300 MHz; $CDCl_3$) 5.58 (1H, dq, *J* 1.1, 0.4), 5.39 (1H, s), 5.19 (1H, qd, *J* 1.4, 1.1), 4.15 (2H, q, *J* 7.2), 1.90 (3H, dd, *J* 1.4, 0.4), 1.27 (3H, t, *J* 7.2), 1.0 (9H, s), 0.15 (6H, s); NMR δ_C (75 MHz; $CDCl_3$) 165.8 (C), 163.1 (C), 140.9 (C), 118.8 (CH_2), 100.2 (CH), 59.4 (CH_2), 25.9 (Me), 19.8 (Me), 18.6 (C), 18.6 (Me), −4.1 (Me).

(*Z*)-Ethyl 4-Methyl-3-(trimethylsiloxy)penta-2,4-dienoate (36).



(*E*)-4-Methoxy-3-methylbut-3-en-2-one[32] (500 mg, 3.20 mmol) in THF (10 mL) was added dropwise to a solution of LDA (4.16 mmol) and TMSCl (0.81 mL, 6.40 mmol) in THF (10 mL) at −78 °C. The resulting pale yellow solution was stirred at the same temperature for 1 h, warmed to rt over 2 h, and concentrated in vacuo without heating. The slurry obtained was diluted with dry *n*-pentane, filtered, and reconcentrated to give the title compound as a slightly turbid colorless oil that was not purified further and was stored in the freezer (725 mg, 99%): NMR δ_H (300 MHz; $CDCl_3$) 5.63 (1H, app. dd, *J* 1.2, 0.7), 5.41 (1H, s), 5.23 (1H, app. t, *J* 1.2), 4.16 (2H, q, *J* 7.2), 1.90 (3H, dd, *J* 1.2, 0.7), 1.28 (2H, t, *J* 7.2), 0.26 (9H, s); NMR δ_C (75 MHz; $CDCl_3$) 166.0 (C), 162.8 (C), 140.5 (C), 119.5 (CH_2), 100.0 (CH), 59.4 (CH_2), 19.5 (Me), 14.4 (Me), 0.53 (Me).

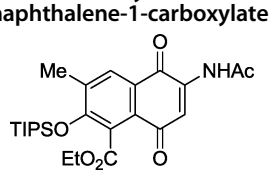
Ethyl 6-Benzamido-3-methyl-5,8-dioxo-2-(triisopropylsiloxy)-5,8-dihydronaphthalene-1-carboxylate (42).



A solution of (*Z*)-ethyl 4-methyl-3-(triisopropylsiloxy)penta-2,4-dienoate (**34**) (165 mg, 0.53 mmol) and 2-benzamido-1,4-benzoquinone (**39**) (100 mg, 0.44 mmol) in dry 1,2-dichlorobenzene (4 mL) was heated to 150 °C for 4 h, cooled, loaded directly onto a column of silica gel, and eluted with ethyl acetate−light petroleum (1:4) to give the title compound as a yellow oil (78 mg, 34%): HRMS found [M + H^+] 536.2463, $C_{30}H_{38}NO_6Si^+$ requires 536.2463; IR ν_{max} ($CHCl_3$)/cm^{-1} 3373, 2949, 2895, 2870, 1730, 1666, 1509, 1489, 1466, 1342, 1328, 1289; UV λ_{max} (CH_2Cl_2)/nm 221 (log ε 4.44), 271 (4.62), 307 (4.72); NMR δ_H (300 MHz; $CDCl_3$) 9.10 (1H, br s), 7.98 (1H, d, *J* 0.5), 7.94 (1H, s), 7.91 (2H, dd, *J* 7.0, 1.3), 7.64−7.51 (3H, m), 4.47 (2H, app. br s), 2.42 (3H, d, *J* 0.5), 1.41 (3H, t, *J* 7.2), 1.37−1.22 (3H, m), 1.14 (18H, d, *J* 7.4); NMR δ_C (75 MHz; $CDCl_3$) 184.5 (C), 180.4 (C). 167.3 (C), 165.8 (C), 156.1 (C), 140.1 (C), 137.7 (C), 133.4 (C), 132.9 (CH), 130.6 (CH), 129.1 (CH), 127.4 (CH), 126.2 (C), 126.1 (C), 125.8 (C), 116.7 (CH), 62.1 (CH_2), 18.4 (Me), 18.0 (Me), 14.4 (CH), 13.8 (Me).

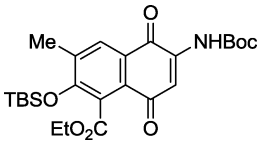
In some instances, aromatization was slow, and after column chromatography, the inseparable aromatized/unaromatized product mixture could be converted into pure **42** by dissolving in dichloromethane and stirring with silica gel under air.

Ethyl 6-Acetamido-3-methyl-5,8-dioxo-2-(triisopropylsiloxy)-5,8-dihydronaphthalene-1-carboxylate (43).



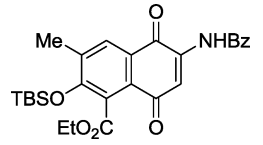
A solution of (*Z*)-ethyl 4-methyl-3-(triisopropylsiloxy)penta-2,4-dienoate (**37**) (230 mg, 0.73 mmol) and 2-acetamido-1,4-benzoquinone (**40**)[22] (100 mg, 0.61 mmol) in dry 1,2-dichlorobenzene (6 mL) was heated to 150 °C for 1 h, cooled, loaded directly onto a column of silica gel, and eluted with ethyl acetate−light petroleum (1:4) to give the title compound as a yellow oil (93 mg, 32%): HRMS found [M + H^+] 474.2307, $C_{25}H_{36}NO_6Si^+$ requires 474.2306; IR ν_{max} ($CHCl_3$)/cm^{-1} 3371, 3097, 2948, 2870, 1726, 1669, 1502, 1342, 1322, 1015; UV λ_{max} (CH_2Cl_2)/nm 226 (log ε 4.39), 272 (4.61), 310 (4.23), 346 (3.69); NMR δ_H (300 MHz; $CDCl_3$) 8.28 (1H, br s), 7.93 (1H, app. d, *J* 0.6), 7.74 (1H, s), 4.43 (2H, br s), 2.40 (3H, d, *J* 0.6), 2.25 (3H, s), 1.39 (3H, t, *J* 7.2), 1.38−1.25 (3H, m), 1.12 (6H, d, 7.3); NMR δ_C (75 MHz; $CDCl_3$) 184.5 (C), 180.2 (C), 169.3 (C), 167.2 (C), 156.0 (C), 139.9 (C), 137.6 (C), 130.4 (CH), 126.1 (C), 126.0 (C), 125.7 (C), 116.6 (CH), 62.0 (CH_2), 25.0 (Me), 18.3 (Me), 18.0 (Me), 14.3 (CH), 13.7 (Me).

Ethyl 6-(*tert*-Butoxycarbonylamino)-2-(*tert*-butyldimethylsiloxy)-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (44).



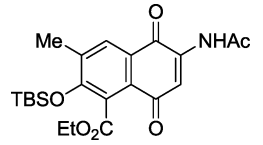
A solution of (*Z*)-ethyl 3-(*tert*-butyldimethylsiloxy)-4-methylpenta-2,4-dienoate (**35**) (106 mg, 0.39 mmol) and 2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**49**)[22] (67 mg, 0.30 mmol) in dry 1,2-dichlorobenzene was heated to 130 °C in a sealed tube in the microwave for 3 h and then loaded directly onto a column of silica gel, eluting with ethyl acetate−light petroleum (1:4), to give the title compound as a yellow tar (97 mg, 66%): HRMS found [M + Na^+] 512.2091, $C_{25}H_{35}NNaO_7Si^+$ requires 512.2075; UV λ_{max} (CH_2Cl_2)/nm 229 (log ε 4.33), 272 (4.58), 311 (4.70), 347 (3.62); NMR δ_H (300 MHz; $CDCl_3$) 7.94 (1H, s), 7.63 (1H, br s), 7.38 (1H, s), 4.44 (2H, q, *J* 7.0), 2.36 (3H, s), 1.51 (9H, s), 1.39 (3H, t, *J* 7.0), 1.00 (9H, s), 0.24 (6H, s); NMR δ_C (75 MHz; $CDCl_3$) 183.9 (C), 179.8 (C), 166.8 (C), 157.7 (C), 151.2 (C), 141.1 (C), 137.5 (C), 130.5 (CH), 126.3 (C), 126.1 (C), 126.0 (C), 114.2 (CH), 82.5 (C), 62.0 (CH_2), 28.1 (Me), 26.0 (Me), 18.8 (C), 18.6 (Me), 13.8 (Me), −2.93 (Me). On a larger scale (1.0 g, 4.47 mmol), the yield was found to decrease considerably (348 mg, 16%).

Ethyl 6-Benzamido-2-(*tert*-butyldimethylsiloxy)-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (45).



A solution of (*Z*)-ethyl 3-(*tert*-butyldimethylsiloxy)-4-methylpenta-2,4-dienoate (**35**) (106 mg, 0.39 mmol) and 2-benzamido-1,4-benzoquinone (**49**)[22] (68 mg, 0.30 mmol) in dry 1,2-dichlorobenzene was heated to 130 °C in a sealed tube in the microwave for 3 h and then loaded directly onto a column of silica gel, eluting with ethyl acetate−light petroleum (1:4) to give the title compound as a yellow solid (39 mg, 26%): mp 151−152 °C; HRMS found [M + Na^+] 516.1822, $C_{27}H_{31}NNaO_6Si^+$ requires 516.1813; IR ν_{max} ($CHCl_3$)/cm^{-1} 3373, 2959, 2934, 2861, 1732, 1699, 1509, 1342, 1328; UV λ_{max} (CH_2Cl_2)/nm 231 (log ε 4.6), 277 (5.0), 314 (4.6); NMR δ_H (400 MHz; $CDCl_3$) 9.11 (1H, br s), 7.99 (1H, app. d, *J* 0.7), 7.93−7.91 (2H, m), 2.64−7.52 (3H, m), 4.49 (2H, br d, *J* 7.0), 2.39 (3H, s), 1.42 (3H, t, *J* 0.7); NMR δ_C (100 MHz; $CDCl_3$) 184.4 (C), 180.4 (C), 166.9 (C), 165.8 (C), 155.0 (C), 140.2 (C), 137.9 (C), 133.4 (C), 132.9 (CH), 130.7 (CH), 129.1 (CH), 127.4 (CH), 166.3 (C), 126.2 (C), 126.1 (C), 116.7 (CH), 62.1 (CH_2), 25.9 (Me), 18.9 (C), 18.7 (Me), 13.9 (Me), −2.6 (Me).

Ethyl 6-Acetamido-2-(*tert*-butyldimethylsiloxy)-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (46).

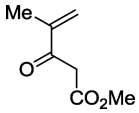


A solution of (*Z*)-ethyl 3-(*tert*-butyldimethylsiloxy)-4-methylpenta-2,4-dienoate (**35**) (106 mg, 0.39 mmol) and 2-acetamido-1,4-benzoquinone (**40**)[22] (50 mg, 0.30 mmol) in dry 1,2-dichlorobenzene (4 mL) was heated to 130 °C in a sealed tube in the microwave for 3 h and

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587−5603

then loaded directly onto a column of silica gel, eluting with ethyl acetate–light petroleum (1:4) to give the title compound as a yellow tar (46 mg, 35%): HRMS found [M + H$^+$] 432.1838, $C_{22}H_{29}NO_6Si^+$ requires 432.1838; IR ν_{max} ($CHCl_3$)/cm^{-1} 3372, 3011, 2960, 2934, 2861, 1729, 2669, 1502, 1351, 1323; UV λ_{max} (CH_2Cl_2)/nm 220 (log ε 4.27), 265 (4.51), 303 (4.12), 343 (3.55); NMR δ_H (300 MHz; $CDCl_3$) 8.26 (1H, br s), 7.95 (1H, d, *J* 0.7), 7.74 (1H, s), 4.45 (2H, q, *J* 7.0), 2.37 (3H, d, *J* 0.7), 2.25 (3H, s), 1.14 (3H, t, *J* 7.0), 1.00 (9H, s), 0.25 (6H, s); NMR δ_C (75 MHz; $CDCl_3$) 184.4 (C), 180.1 (C), 169.3 (C), 166.8 (C), 155.0 (C), 139.9 (C), 137.8 (C), 130.6 (CH), 126.1 (C), 125.9 (C), 116.5 (C), 62.0 (CH_2), 25.7 (Me), 25.0 (Me), 18.7 (Me), 13.8 (Me), −2.9 (Me).

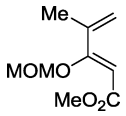
Methyl 4-Methyl-3-oxopent-4-enoate (47).



This compound was prepared according to the literature procedure for the corresponding ethyl ester.[32]

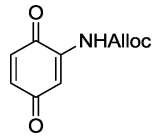
Thus, triethylamine (18.46 mL, 140.86 mmol) and anhydrous magnesium chloride (6.71 g, 70.43 mmol) were added to a suspension of methyl potassium malonate (10.0 g, 64.03 mmol) in acetonitrile (100 mL) at 0 °C. The thick white suspension was stirred at this temperature for 30 min, becoming solid and immobile. Methacryloyl chloride (3.13 mL, 32.01 mmol) was then added dropwise, with swirling of the reaction flask by hand. After the addition was complete, the resulting clear yellow solution was stirred for 30 min at 0 °C, cold hydrochloric acid (1 M; 100 mL) was added, and the reaction mixture was stirred for a further 45 min at the same temperature. Water (100 mL) was added, and the aqueous phase was extracted with ether (3 × 100 mL). The combined extracts were washed with water (200 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated. The resulting pale brown oil was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:9), to give the title compound as a colorless liquid (1.78 g, 39%): IR ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2956, 1743, 1522, 1439, 1329, 1240; NMR δ_H (400 MHz; $CDCl_3$; data given for major keto-form) 5.96 (1H, d, *J* 0.8), 5.90 (1H, q, *J* 1.5), 3.75 (2H, s), 3.74 (3H, s), 1.90 (3H, dd, *J* 1.5, 0.8); NMR δ_H (100 MHz; $CDCl_3$; data given for major keto-form) 194.0 (C), 168.2 (C), 144.1 (C), 126.8 (CH_2), 120.2 (CH_2), 52.4 (Me), 44.8 (CH_2), 17.4 (Me).

(*Z*)-Methyl 3-Methoxymethoxy-4-methylpenta-2,4-dienoate (48).



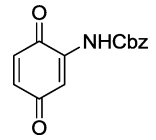
DBU (358 μL, 2.40 mmol) was slowly added to a solution of methyl 4-methyl-3-oxopent-4-enoate (**50**) (284 mg, 2.00 mmol) and chloromethyl methyl ether (167 μL, 2.40 mmol) in toluene (10 mL), and the turbid solution was heated to 80 °C. After 30 min, the reaction mixture was cooled to rt, and brine (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were dried (Na_2CO_3) and concentrated. The residue was purified by flash column chromatography on a short (10 cm) column of silica gel, eluting with ethyl acetate–light petroleum (1:9) to give the title compound as a colorless oil (312 mg, 70%): HRMS found [M + Na$^+$] 209.0796, $C_9H_{14}NaO_4^+$ requires 209.0784; IR ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2955, 2846, 1741, 1680, 1637, 1438, 1240, 1161; NMR δ_H (400 MHz; $CDCl_3$) 5.78 (1H, br s), 5.51 (1H, s), 5.34 (1H, m), 5.13 (2H, s), 3.74 (3H, s), 3.56 (3H, s), 1.93 (3H, q, *J* 1.3); NMR δ_C (100 MHz; $CDCl_3$) 166.7 (C), 165.8 (C), 138.8 (C), 120.5 (CH_2), 101.3 (CH), 99.9 (CH_2), 57.6 (Me), 51.2 (Me), 19.7 (Me).

2-Allyloxycarbonylamino-1,4-benzoquinone (49).



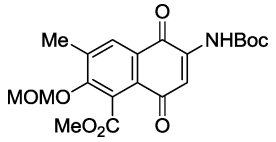
Di(acetoxy)iodobenzene (1.70 g, 5.27 mmol) was added to a stirred suspension of allyl (2,5-dimethoxyphenyl)carbamate[44] (500 mg, 2.11 mmol) in water (20 mL)–methanol (0.5 mL). The reaction mixture was stirred for 3 h, the aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution (20 mL), water (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:9–1:4) to give the title compound as an orange oil (108 mg, 22%): HRMS found [M + Na$^+$] 230.0414, $C_{10}H_9NNaO_4^+$ requires 230.0424; IR ν_{max} ($CHCl_3$)/cm^{-1} 3375, 3012, 2955, 1746, 1674, 1651, 1326, 1193; UV λ_{max} (CH_2Cl_2)/nm 228 (log ε 3.9), 260 (4.0), 383 (3.2); NMR δ_H (400 MHz; $CDCl_3$) 7.62 (1H, br s), 7.29 (1H, d, *J* 2.3), 6.82 (1H, d, *J* 10.0), 6.76 (1H, dd, *J* 10.0, 2.3), 5.97 (1H, ddt, *J* 17.1, 10.5, 5.8), 5. 41 (1H, dq, *J* 17.1, 1.4), 5.34 (1H, dq, *J* 10.5, 1.4), 4.72 (1H, dt, *J* 5.8, 1.4). NMR δ_C (100 MHz; $CDCl_3$) 187.3 (C), 182.1 (C), 151.9 (C), 139.0 (C), 138.2 (CH), 133.2 (CH), 131.4 (CH), 119.3 (CH_2), 113.2 (CH), 66.9 (CH_2).

2-Benzyloxycarbonylamino-1,4-benzoquinone (50).



Di(acetoxy)iodobenzene (2.47 g, 7.66 mmol) was added to a stirred suspension of benzyl (2,5-dimethoxyphenyl)carbamate (1.00 g, 3.48 mmol) in water (35 mL) and methanol (0.88 mL). The reaction mixture was stirred for 3 h, the aqueous phase was extracted with ethyl acetate (3 × 30 mL), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution (30 mL), water (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:9–1:4) to give the title compound as a yellow powder (164 mg, 18%): mp 88–89 °C; HRMS found [M + Na$^+$] 280.0580, $C_{14}H_{11}NNaO_4^+$ requires 280.0578; IR ν_{max} ($CHCl_3$)/cm^{-1} 3374, 3094, 3045, 2963, 1746, 1674, 1651, 1599, 1327, 1192, 1026; UV λ_{max} (CH_2Cl_2)/nm 228 (log ε 4.2), 259 (4.3), 380 (3.5); NMR δ_H (400 MHz; $CDCl_3$) 7.63 (1 H, br s), 7.44–7.39 (5H, m), 7.31 (1H, d, *J* 2.0), 6.81 (1H, d, *J* 10.0), 6.76 (1H, dd, *J* 10.0, 2.0); δ_c (100 MHz; $CDCl_3$) 187.3 (C), 182.1 (C), 152.0 (C), 139.0 (C), 138.2 (CH), 145.0 (C), 133.2 (CH_2), 128.81 (CH), 128.77 (CH), 128.5 (CH), 133.2 (CH), 68.1 (CH_2).

Methyl 6-(*tert*-Butoxycarbonylamino)-2-methoxymethoxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (51).

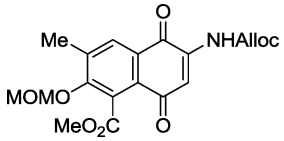


A solution of (*Z*)-methyl 3-methoxymethoxy-4-methylpenta-2,4-dienoate (**48**) (97 mg, 0.45 mmol) and 2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**38**)[22] (67 mg, 0.30 mmol) in dry 1,2-dichlorobenzene (2 mL) was heated to 130 °C in a sealed tube in the microwave for 3 h. The reaction mixture was then diluted with EtOAc (10 mL), treated with silica gel (ca. 4 g), and stirred under air for 24 h. Ethyl acetate was removed under reduced pressure, and the remaining solution of crude product in 1,2-dichlorobenzene was loaded directly onto a column of silica gel and eluted with ethyl acetate–light petroleum (1:4) to give the title compound as a yellow tar (24 mg, 20%): HRMS found [M + Na$^+$], 428.1342.

dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

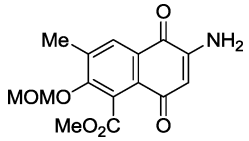
$C_{20}H_{23}NNaO_8^+$ requires 428.1326; IR ν_{max} ($CHCl_3$)/cm^{-1} 2984, 1795, 1736, 1673, 1648, 1506, 1148, 908; UV λ_{max} (CH_2Cl_2)/nm 229 (log ε 4.0), 268 (4.2), 306 (3.9); NMR δ_H (400 MHz; $CDCl_3$) 8.08 (1H, s), 7.62 (1H, br s), 7.45 (1H, s), 5.10 (2H, s), 4.02 (3H, s), 3.61 (3H, s), 2.49 (3H, s), 1.54 (9H, s); NMR δ_C (100 MHz; $CDCl_3$) 183.7 (C), 179.6 (C), 167.3 (C), 156.9 (C), 151.1 (C), 141.2 (C), 140.8 (C), 130.6 (CH), 128.5 (C), 128.4 (C), 126.2 (C), 114.4 (CH), 100.8 (CH_2), 82.7 (C), 57.8 (Me), 53.0 (Me), 28.1 (Me), 14.9 (Me).

Methyl 6-(Allyloxycarbonylamino)-2-methoxymethoxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (53).



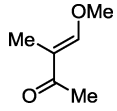
A solution of (*Z*)-methyl 3-methoxymethoxy-4-methylpenta-2,4-dienoate (**48**) (65 mg, 0.30 mmol) and 2-allyloxycarbonylamino-1,4-benzoquinone (**50**) (42 mg, 0.20 mmol) in 1,2-dichlorobenzene (2 mL) was heated to 130 °C in a sealed tube in the microwave for 3 h and then loaded directly onto a column of silica gel, eluting with ethyl acetate–light petroleum (1:4) to give the title compound as a yellow tar (37 mg, 47%): HRMS found [M + Na^+], 412.1026. $C_{19}H_{19}NNaO_8^+$ requires 412.1003; IR ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1741, 1672, 1511, 1464, 1327; UV λ_{max} (CH_2Cl_2)/nm 227 (log ε 4.1), 267 (4.3), 305 (4.0); NMR δ_H (400 MHz; $CDCl_3$) 8.02 (1H, br d, *J* 0.8), 7.83 (1H, br s), 7.47 (1H, s), 5.95 (1H, ddt, *J* 17.2, 10.3, 5.7), 5.39 (1H, dq, *J* 17.2, 1.2), 5.31 (1H, dq *J* 10.3, 1.2), 5.09 (2H, s), 4.71 (2H, dt, *J* 5.7, 1.2), 4.01 (3H, s), 3.60 (3H, s), 2.48 (3H, d, *J* 0.8); NMR δ_C (100 MHz; $CDCl_3$) 183.6 (C), 179.3 (C), 167.3 (C), 157.0 (C), 151.9 (C), 141.0 (C), 140.8 (C), 131.4 (CH), 130.7 (CH), 128.6 (C), 128.4 (C), 126.1 (C), 119.2 (CH_2), 115.1 (CH), 100.9 (CH_2), 66.9 (CH_2), 57.8 (Me), 52.2 (Me), 17.7 (Me).

Methyl 6-Amino-2-methoxymethoxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (31).



Tetrakis(triphenylphosphine)palladium(0) (7 mg, 0.006 mmol) and dimedone (168 mg, 0.120 mmol) were added to a solution of methyl 6-(allyloxycarbonylamino)-2-methoxymethoxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylate (**53**) (20 mg, 0.060 mmol) in THF (5 mL), and the resulting orange solution was stirred at rt for 30 min and then poured into saturated aqueous sodium hydrogen carbonate solution (10 mL). The resulting aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (8:2) to give the title compound as a red film (11 mg, 60%) whose data matched those reported above.

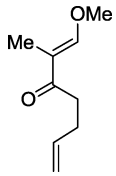
***(E)*-4-Methoxy-3-methylbut-3-en-2-one (54).**



Butanone (25 mL, 280.8 mmol) was added dropwise over 10 min to a 0 °C suspension of sodium hydride (60% dispersion in mineral oil; 16.85 g, 421.2 mmol) and methyl formate (51.6 mL, 642 mmol) in THF (500 mL). The reaction mixture was stirred for 75 min and concentrated under reduced pressure, and the solid obtained was redissolved immediately in DMF (200 mL) and cooled to 0 °C. Dimethyl sulfate (53.3 mL, 561.6 mmol) was then slowly added (CAUTION: very exothermic), and the resulting brown solution was warmed to rt and stirred for 16 h. Water (1 L) was added, and the aqueous phase was extracted with ether (3 × 300 mL). The combined extracts were washed with aqueous ammonia solution (33%; 300 mL), water (4 × 500 mL), and brine (500 mL), dried ($MgSO_4$), and concentrated. The residue was purified by double distillation under reduced pressure to give the title compound as a colorless oil that darkens upon standing and was stored in the freezer at −18 °C (14.3 g, 45%): bp 40–45 °C/2 mmHg (lit.[45] bp 62–64 °C/4 mmHg); NMR δ_H (300 MHz; $CDCl_3$) 7.22 (1H, q, *J* 1.2), 3.88 (3H, s), 2.22 (3H, s), 1.71 (3H, d, *J* 1.2); NMR δ_C (75 MHz; $CDCl_3$) 197.5 (C), 160.3 (CH), 117.8 (C), 61.3 (Me), 25.3 (C), 8.2 (Me). The data obtained matched those reported.[46]

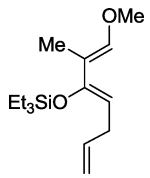
Note: It is important that a vacuum pump is used for the distillation as a water aspirator does not provide sufficient vacuum to allow distillation to occur without significant thermal decomposition. The product was typically obtained as a mixture with the other regioisomer, which can be separated by careful distillation through a 30 cm Vigreux column, or column chromatography, but small amounts (<10%) do not affect subsequent reactions.

***(E)*-1-Methoxy-2-methylhepta-1,6-dien-3-one (55).**



A solution of (*E*)-4-methoxy-3-methylbut-3-en-2-one (**54**) (2.0 g, 17.52 mmol) in THF (50 mL) was added dropwise to a −78 °C solution of LDA (19.27 mmol) in THF (100 mL). After 2 h at −78 °C, DMPU (2.32 mL, 19.27 mmol) and allyl iodide (2.40 mL, 26.28 mmol) were added, and the reaction stirred for a further 30 min at this temperature. The yellow solution was warmed to rt, stirred for 2 h, and then quenched by addition of saturated aqueous ammonium chloride solution (100 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (5:95) to give the title compound as a pale yellow oil (1.33 g, 49%): HRMS found [M + Na^+] 177.0881, $C_9H_{14}NaO_2^+$ requires 177.0886; IR ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2940, 1737, 1714, 1449, 1374, 1240, 1112; NMR δ_H (300 MHz; $CDCl_3$) 7.24 (1H, q, *J* 1.2), 5.84 (1H, ddt, *J* 17.1, 10.3, 6.5), 5.04 (1H, app. dq, *J* 17.1, 1.5), 4.97 (1H, app. dq, *J* 10.3, 1.5), 3.87 (3H, s), 2.61 (2H, t, *J* 7.0), 2.37 (2H, tdt, *J* 7.0, 6.5, 1.5), 1.72 (3H, d, *J* 1.1); NMR δ_C (75 MHz; $CDCl_3$) 199.0 (C), 159.4 (C), 137.7 (CH_2), 117.2 (CH), 61.3 (Me), 36.6 (CH_2), 28.9 (CH_2), 8.4 (Me).

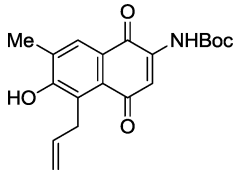
(1*E*,3*Z*)-Triethyl(1-methoxy-2-methylhepta-1,3,6-trien-3-yloxy)silane (56).



(*E*)-1-Methoxy-2-methylhepta-1,6-dien-3-one (**55**) (748 mg, 4.85 mmol) in THF (10 mL) was added to LDA (17.2 mmol) in THF (40 mL) and chlorotriethylsilane (4.80 mL, 28.6 mmol) at −78 °C, stirred at this temperature for 30 min, and warmed to rt. The reaction mixture was concentrated without heating, diluted with dry *n*-pentane (50 mL), filtered, and concentrated to give the title compound as a yellow oil that could not be purified and was stored in the freezer at −18 °C (2.1 g, 62%): NMR δ_H (300 MHz; $CDCl_3$) 5.89–5.74 (1H, m), 5.23 (1H, br s, CH), 5.10–4.85 (3H, m), 2.89 (2H, app t, *J* 6.4), 1.85 (3H, s), 1.00–0.65 (15H, m). Due to the instability of this compound, meaningful ^{13}C, IR, and MS data could not be obtained.

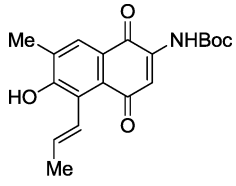
dx.doi.org/10.1021/jo400737f | J. Org. Chem. 2013, 78, 5587–5603

***tert*-Butyl (5-Allyl-6-hydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (57).**



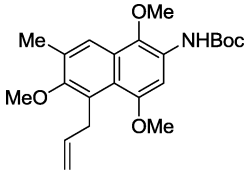
(1*E*,3*Z*)-Triethyl(1-methoxy-2-methylhepta-1,3,6-trien-3-yloxy)silane (**56**) (180 mg, 0.67 mmol) was added to 2-*tert*-butoxycarbonylamino-1,4-benzoquinone (**38**)[22] (100 mg, 0.45 mmol) in dichloromethane (3 mL) at rt, and the brown solution was stirred for 1 h. Silica gel was added, and the reaction mixture was stirred under air for 6 h, concentrated, and purified by flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:4) to give the title compound as a yellow solid (148 mg, 96%): mp 169–173 °C; HRMS found [M + H^+] 343.3737, $C_{19}H_{22}NO_5^+$ requires 343.3737; IR ν_{max} ($CHCl_3$)/cm^{-1} 3470, 3378, 3013, 2985, 2936, 1737, 1661, 1636, 1507, 1339, 1152; UV λ_{max} (CH_2Cl_2)/nm 228 (log ε 4.35), 272 (4.36), 312(4.24), 357 (3.75); NMR δ_H (400 MHz; $CDCl_3$) 7.89 (1H, app. d, *J* 0.6), 7.63 (1H, br s), 7.28 (1H, s), 6.09–5.99 (1H, m), 5.17–5.12 (2H, m), 4.09 (2H, dt, *J* 6.0, 1.6), 2.35 (3H, d, *J* 0.6), 1.53 (9H, s); NMR δ_C (100 MHz; $CDCl_3$) 187.3 (C), 180.2 (C), 159.7 (C), 151.4 (C), 139.7 (C), 135.5 (CH), 129.4 (C), 129.3 (CH), 129.3 (C), 126.4 (C), 124.5 (C), 116.5 (CH), 116.4 (CH_2), 82.4 (C), 30.4 (CH_2), 28.1 (Me), 16.4 (Me).

***(E)*-*tert*-Butyl (6-Hydroxy-7-methyl-1,4-dioxo-5-(prop-1-en-1-yl)-1,4-dihydronaphthalen-2-yl)carbamate (58).**



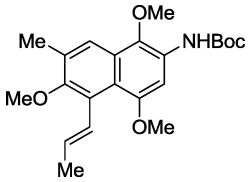
A solution of *tert*-butyl (5-allyl-6-hydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (**57**) (100 mg, 0.284) and bis(acetonitrile)dichloropalladium(II) (4 mg, 0.011 mmol, 5 mol %) in CH_2CH_2 (10 mL) was heated to reflux and stirred for 2 h. The reaction mixture was concentrated and adsorbed on to silica gel. The residue was purified by flash column chromatography on silica gel eluting with toluene to give the title compound as a pale orange solid (37 mg, 37%): HRMS found [M + H^+] 366.1327, $C_{19}H_{21}NO_5^+$ requires 366.1312; IR ν_{max} 3468, 3375, 3012, 2984, 2984, 1735, 1659, 1506, 1110; UV λ_{max} (CH_2Cl_2)/nm 228 (log ε 4.6), 267 (4.4), 315 (4.5), 364 (3.9); NMR δ_H ($CDCl_3$, 400 MHz) 7.86 (1H, s), 7.67 (1H, br s), 7.25 (1H, s), 6.80 (1H, dq, *J* 16.6, 1.7), 5.86 (1H, dq, *J* 16.6, 6.5), 2.34 (3H, s), 2.04 (3H, dd, *J* 6.5, 1.7), 1.53 (9H, s); NMR δ_C ($CDCl_3$, 100 MHz) 186.4 (C), 180.1 (C), 157.3 (C), 151.4 (C), 139.9 (C), 130.7 (CH), 129.5 (CH), 128.3 (C), 124.3 (C), 123.3 (C), 115.5 (CH), 82.3 (C), 28.1 (Me), 18.8 (Me), 16.7 (Me).

***tert*-Butyl (5-Allyl-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)carbamate (59).**



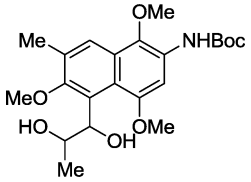
A solution of *tert*-butyl (5-allyl-6-hydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (**57**) (700 mg, 2.014 mmol) and cerium(III) chloride heptahydrate (1.14 g, 3.06 mmol) in THF (70 mL) and water (35 mL) was degassed by sparging with argon in a sonic bath for 10 min. Sodium borohydride (154 mg, 4.08 mmol) was then added portionwise over 5 min, and the reaction mixture was stirred until it became colorless and the evolution of hydrogen gas ceased. Dimethyl sulfate (3.87 mL, 40.08 mmol) was then added, followed by a solution of potassium hydroxide (2.25 g, 40.08 mmol) in degassed water (35 mL), causing the almost colorless solution to become dark purple. The reaction mixture was stirred for 16 h at rt, and the quenched by the addition of aqueous ammonium hydroxide solution (20 mL) and water (50 mL). The aqueous phase was extracted with ether (4 × 50 mL), and the combined ethereal extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate–light petroleum (1:49–1:19) to give the title compound as a light brown solid (690 mg, 93%): mp 81–82 °C; HRMS found [M + Na^+], 410.1938. $C_{22}H_{29}NNaO_5^+$ requires 410.1951; IR ν_{max} ($CHCl_3$)/cm^{-1} 3425, 3011, 2982, 2940, 1720, 1625, 1492, 1457, 1158, 1061; NMR δ_H (400 MHz; $CDCl_3$) 7.76 (1H, br s), 7.68 (1H, app. d, *J* 0.8), 7.14 (1H, s), 6.16 (1H, ddt, *J* 17.1, 10.3, 5.8), 4.97–4.90 (2H, m), 4.14 (2H, dt, *J* 5.8, 1.6), 3.95 (3H, s), 3.86 (3H, s), 3.80 (3H, s), 2.50 (3H, d, *J* 0.8); NMR δ_C (100 MHz; $CDCl_3$) 154.4 (C), 154.0 (C), 152.9 (C), 139.9 (C), 135.3 (C), 131.9 (C), 128.4 (C), 127.0 (C), 126.4 (C), 121.1 (CH), 120.9 (C), 113.5 (CH_2), 98.5 (CH), 80.6 (C), 61.2 (Me), 61.1 (Me), 55.6 (Me), 32.3 (CH_2), 28.4 (CH), 17.4 (Me).

***(E)*-*tert*-Butyl (1,4,6-Trimethoxy-7-methyl-5-(prop-1-en-1-yl)-naphthalen-2-yl)carbamate (60).**



To a solution of *tert*-butyl (5-allyl-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)carbamate (**59**) (230 mg, 0.50 mmol) in THF (10 mL) was added potassium *tert*-butoxide (575 mg, 5.1 mmol), and the resulting deep purple solution was heated to 80 °C in a sealed tube for 3 h using a microwave reactor. The resulting brown solution was poured into hydrochloric acid (1 M; 10 mL), and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to give the title compound as a brown oil that did not require further purification (193 mg, 84%): mp 98–99 °C; HRMS found [M + Na^+] 410.1960, $C_{22}H_{29}NNaO_5^+$ requires 410.1951; IR ν_{max} ($CHCl_3$)/cm^{-1} 3425, 3011, 2983, 2936, 1720, 1624, 1490, 1457, 1159; NMR δ_H (400 MHz; $CDCl_3$) 7.75 (1H, br s), 7.65 (1H, s), 7.14 (1 H, s), 6.79 (1H, dq, *J* 15.9, 1.7), 5.82 (1H, dq, *J* 15.9, 6.5), 3.92 (3H, s), 3.86 (3H, s), 3.69 (3H, s), 2.48 (3H, d, *J* 0.8), 1.97 (3H, dd, *J* 6.5, 1.7); NMR δ_C (100 MHz; $CDCl_3$) 154.2 (C), 154.0 (C), 152.9 (C), 135.5 (C), 132.4 (C), 127.7 (C), 127.2 (CH), 127.1 (CH), 127.0 (CH), 125.8 (C), 121.1 (CH), 99.7 (CH), 80.6 (C), 61.3 (Me), 69.6 (Me), 56.3 (Me), 28.4 (Me), 19.0 (Me), 17.5 (Me).

***tert*-Butyl (5-(1,2-Dihydroxypropyl)-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)carbamate.**

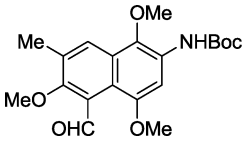


N-Methylmorpholine *N*-oxide (46 mg, 0.344 mmol) and osmium tetraoxide (2.5 wt % in *t*-BuOH; 84 mL, 0.066 mmol) were added to a solution of (*E*)-*tert*-butyl (1,4,6-trimethoxy-7-methyl-5-(prop-1-en-1-yl)naphthalen-2-yl)carbamate (**60**) (120 mg, 0.328 mmol) in THF-*t*-BuOH–water (10:8:1; 19 mL), and the brown solution was stirred at rt for 2 d. Saturated aqueous sodium thiosulfate solution (10 mL) and the reaction mixture were stirred for 30 min, diluted with water (20 mL), and extracted with ethyl acetate (5 × 20 mL). The combined extracts were washed with sodium thiosulfate solution, water, and brine, dried ($MgSO_4$), and concentrated to give the title compound as a brown tar that was used without further purification (110 mg, 83%): HRMS found [M + Na^+] 444.2018, $C_{22}H_{31}NNaO_7^+$ requires 444.1993; IR ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3008, 2983, 2940, 1720, 1628, 2507, 1491, 1457, 1369, 1240, 1156, 1063; NMR δ_H (400 MHz;

dx.doi.org/10.1021/jo400737f | *J. Org. Chem.* 2013, 78, 5587–5603

$CDCl_3$) 7.96 (1H, br s), 7.81 (1H, s), 7.15 (1H, s), 5.38 (1H, br d, *J* 7.5), 4.84 (1H, br s), 4.14 (1H, dq, *J* 7.5, 6.3), 4.09 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 2.49 (3H, s), 1.60 (9H, s), 0.85 (3H, d, *J* 6.3); NMR δ_C (100 MHz; $CDCl_3$) 156.2 (C), 152.9 (C), 147.0 (C), 136.3 (C), 132.2 (C), 127.34 (C), 127.25 (C), 126.8 (C), 123.5 (CH), 119.4 (C), 110.4 (C), 99.8 (CH), 81.0 (C), 74.3 (CH), 70.6 (CH), 61.9 (Me), 61.4 (Me), 56.0 (Me), 28.4 (Me), 19.0 (Me), 17.7 (Me).

6-*tert*-Butoxycarbonylamino-2,5,8-trimethoxy-3-methylnaphthalene-1-carboxaldehyde (61).



Sodium periodate (120 mg, 0.55 mmol) was added to crude *tert*-butyl (5-(1,2-dihydroxypropyl)-1,4,6-trimethoxy-7-methylnaphthalen-2-yl)-carbamate from the previous reaction (110 mg, 0.28 mmol) in 1:1 THF–water (10 mL), and the pale brown solution was stirred under air at rt for 14 h. Water (30 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Flash column chromatography on silica gel eluting with ethyl acetate–light petroleum (1:9) gave the title compound as an off-white solid (50 mg, 48%): mp 112–113 °C; HRMS found [M + Na^+] 398.1603, $C_{20}H_{25}NNaO_6^+$ requires 398.1574; IR ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3008, 2939, 2858, 1723, 1706, 1629, 1499, 1462, 1242, 1162, 1148, 1071; NMR δ_H (400 MHz; $CDCl_3$) 10.73 (1H, s), 7.82 (1H, br s), 7.81 (1H, s), 7.16 (1H, br s), 3.97 (3H, s), 3.874 (3H, s), 3.867 (3H, s), 2.49 (3H, d, *J* 1.2), 1.59 (9H, s); NMR δ_C (125 MHz; $CDCl_3$) 194.6 (CH), 153.4 (C), 152.8 (C), 151.7 (C), 135.5 (C), 132.8 (C), 128.4 (C), 128.1 (C), 125.2 (C), 124.7 (CH), 118.9 (C), 99.0 (CH), 80.9 (C), 63.3 (Me), 61.5 (Me), 56.2 (Me), 28.4 (Me), 16.8 (Me).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, X-ray crystallographic data of naphthoate **26**, computational results and related data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: c.j.moody@nottingham.ac.uk. Fax: (+44)115 9513564.

Author Contributions

†C.C.N. and L.I.P. contributed equally to the work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for funding (DTA studentships to C.C.N. and L.I.P.).

■ REFERENCES

(1) Thomson, R. H. *Naturally Occurring Quinones IV. Recent Advances*, 4th ed.; Blackie: London, 1997.
(2) O'Brien, R. J.; Lyle, M. A.; Snider, D. E. *Rev. Infect. Dis.* **1987**, *9*, 519–530.
(3) Brogden, R. N.; Fitton, A. *Drugs* **1994**, *47*, 983–1009.
(4) Matsuda, S.; Adachi, K.; Matsuo, Y.; Nukina, M.; Shizuri, Y. *J. Antibiot.* **2009**, *62*, 519–526.
(5) Cai, P.; Kong, F.; Ruppen, M. E.; Glasier, G.; Carter, G. T. *J. Nat. Prod.* **2005**, *68*, 1736–1742.
(6) Hanessian, S.; Wang, W.; Gai, Y.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034–10041.
(7) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293–1296.
(8) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331–11332.
(9) Canova, S.; Bellosta, V.; Bigot, A.; Mailliet, P.; Mignani, S.; Cossy, J. *Org. Lett.* **2006**, *9*, 145–148.
(10) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Soma Sekhar, B. B. V.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549–3552.
(11) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888.
(12) Qin, H.-L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477–2479.
(13) Turks, M.; Huang, X.; Vogel, P. *Chem.—Eur. J.* **2005**, *11*, 465–476.
(14) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862–867.
(15) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525.
(16) Li, J.; Menche, D. *Synthesis* **2009**, 2293–2315.
(17) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163–1180.
(18) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965–7967.
(19) Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R.; Golen, J. A.; Rheingold, A. L. *Tetrahedron Lett.* **2013**, *54*, 2615–2618.
(20) Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis* **1990**, 142–144.
(21) Jamie, J. F.; Rickards, R. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2603–2613.
(22) Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872–7881.
(23) Becker, A. M.; Herlt, A. J.; Hilton, G. L.; Kibby, J. J.; Rickards, R. W. *J. Antibiot.* **1983**, *36*, 1323–1328.
(24) Kibby, J. J.; McDonald, I. A.; Rickards, R. W. *J. Chem. Soc., Chem. Commun.* **1980**, 768–769.
(25) Anderson, M. G.; Monypenny, D.; Rickards, R. W.; Rothschild, J. M. *J. Chem. Soc., Chem. Commun.* **1989**, 311–313.
(26) Sensi, P. *Pure Appl. Chem.* **1975**, *41*, 15–31.
(27) Rickards, R. W. *Stud. Nat. Prod. Chem.* **1991**, *9*, 431–445.
(28) Baytekin, B.; Baytekin, H. T.; Hahn, U.; Reckien, W.; Kirchner, B.; Schalley, C. A. *Chem.—Eur. J.* **2009**, *15*, 7139–7149.
(29) Crombie, L.; Jamieson, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1467–1475.
(30) Nawrat, C. C.; Moody, C. J. *Org. Lett.* **2012**, *14*, 1484–1487.
(31) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142–143.
(32) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053–5056.
(33) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070–1073.
(34) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207–210.
(35) Elban, M. A.; Hecht, S. M. *J. Org. Chem.* **2008**, *73*, 785–793.
(36) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481–5484.
(37) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
(38) Becker, A. M.; Rickards, R. W. *Aust. J. Chem.* **1984**, *37*, 2103–2109.
(39) Shi, F.; Smith, M. R.; Maleczka, R. E. *Org. Lett.* **2006**, *8*, 1411–1414.
(40) Chakraborty, T. K.; Reddy, G. V. *J. Org. Chem.* **1992**, *57*, 5462–5469.
(41) Lin, C.-F.; Yang, J.-S.; Chang, C.-Y.; Kuo, S.-C.; Lee, M.-R.; Huang, L.-J. *Bioorg. Med. Chem.* **2005**, *13*, 1537–1544.
(42) Choudhury, A. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 132–134.
(43) Michaelides, M. R.; Schoenleber, R.; Thomas, S.; Yamamoto, D. M.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2946–2953.
(44) Wipf, P.; Kim, Y. T.; Jahn, H. *Synthesis* **1995**, 1549.
(45) Sugasawa, S.; Yamada, S.-i.; Narahashi, M. *Yakugaku Zasshi* **1951**, *71*, 1345–1349.
(46) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976–4977.