JOC The Journal of Organic Chemistry

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Regioselective Cope Rearrangement and Prenyl Transfers on Indole Scaffold Mimicking Fungal and Bacterial Dimethylallyltryptophan Synthases †

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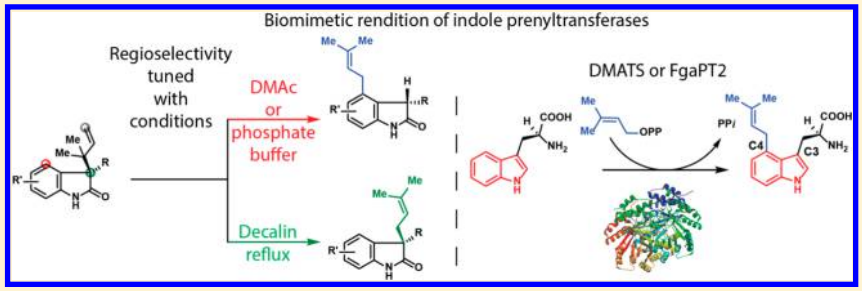
Supporting Information



ABSTRACT: Aromatic prenyltransferases are an actively mined enzymatic class whose biosynthetic repertoire is growing. Indole prenyltransferases catalyze the formation of a diverse set of prenylated tryptophan and diketopiperazines, leading to the formation of fungal toxins with prolific biological activities. At a fundamental level, the mechanism of C4-prenylation of L-tryptophan recently has surfaced to engage a debate between a "direct" electrophilic alkylation mechanism (for wt DMATS and FgaPT2) versus an indole C3−C4 "Cope" rearrangement followed by rearomatization (for mutant FgaPT2). Herein we provide the first series of regioselectively tunable conditions for a Cope rearrangement between C3 and C4 positions. Biomimetic conditions are reported that effect a [3,3]-sigmatropic shift whose two-step process is interrogated for intramolecularity and rate-limiting general base-promoted mechanism. Solvent polarity serves a crucial role in changing the regioselectivity, resulting in sole [1,3]-shifts under decalin. An intermolecular variant is also reported that effectively prenylates the C3 position of L-tryptophan, resulting in products that mimic the structures accessed by bacterial indole prenyltransferases. We report an elaborate investigation that includes screening various substituents and measuring steric and electronic effects and stereoselectivity with synthetically useful transformations.

INTRODUCTION

Prenyltransferases are an extensive family of enzymes responsible for activating and modifying isoprenoids (C_5, C_{10}, C_{15}, C_{20}, etc.) for the biosynthesis of diverse secondary metabolites. Aromatic prenyltransferases are an actively mined enzymatic class whose biosynthetic repertoire is growing. Tryptophan-containing alkaloids and peptidyl natural products are prenylated by a monophyletic subclass of aromatic prenyltransferases in fungi, cyanobacteria, and a few plants.[1] *Claviceps purpurea* dimethylallyltryptophan synthase (DMATS) catalyzes the committed step toward formation of C4-dimethylallyltryptophan (**1**) from L-tryptophan (L-Trp) and dimethylallyl diphosphate (DMAPP), as represented in Figure 1.[2−5]

This step is a crucial biosynthetic event leading to the formation of structurally diverse C4-prenylated alkaloid natural products. Late-stage modifications on **1** lead to divergent pathways toward ergot and clavine alkaloids, and their specificity is organism-dependent.[6−8] Evolutionarily related DMATS species, also referred to as indole prenyl transferases (PTs), have been identified and biochemically characterized from multiple genera of fungi[1,9−30] and other microbial systems.[31−36] The underlying mechanistic dichotomy between a direct C4-prenylation on the indole nucleus (through an electrophilic aromatic substitution[3,37]) and a C3-reverse prenylation followed by a Cope rearrangement−tautomerization sequence (recently brought to light by Tanner et al.[27,28,38,39]) still lingers, depending on the nature of the enzyme one investigates. Proposed biosynthetic formalisms predated even the initial discovery and biochemical characterization of *Claviceps purpurea* DMATS gene.[40,41] Mechanistic speculations have spurred experimental research for over three decades, with synthetic models originating from the laboratories of Arigoni,[42] Wenkert,[43] and Jackson,[44−47] leading up to recent reports of elegant mechanistic probes developed by Gaich and co-workers[48,49] (Scheme 1A, B).

In the pregenomic era, the structure of echinulin, a fungal prenylated tryptophan alkaloid, soon after its disclosure generated active interest from synthetic chemists attempting

Received: July 21, 2014
Published: September 22, 2014

   dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

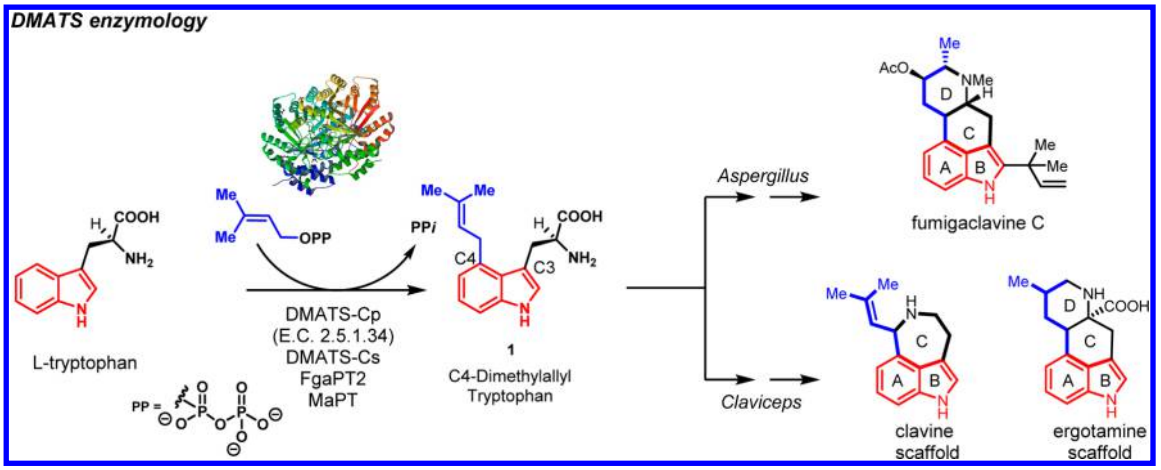


Figure 1. Enzymatic reaction catalyzed by C4-dimethylallyltryptophan synthase (4-DMATS) and its biosynthetic context toward clavine and ergotamine alkaloid formation in multiple fungal organisms.

to offer a mechanistic rationale for its biosynthesis. The direct C4 electrophilic alkylation mechanism originally proposed (and experimentally verified) for the *Claviceps* 4-DMATS enzyme by Poulter et al. recently has received a rejuvenated interest. The position isotope exchange (PIX) experiments[38,39] along with the substitution studies on wild-type *Claviceps* 4-DMATS[37] added further evidence for a direct C4 electrophilic alkylation of L-Trp. The discovery of a C3-reverse prenylated pyrroloindoline product under a Lys174Ala mutant of FgaPT2 enzyme raised the possibility of a potential C3- to C4-Cope rearrangement as a mechanistic model.[39] In the postgenomic era, nearly 200 gene candidates that share significant sequence similarity to DMATS are identifiable in publicly available genomes. While the synthetic endeavors reported by Voute et al.[50] and Gaich et al.[48,49] (as shown in Scheme 1B) provided some insight into the feasibility of models proposed earlier by Arigoni,[42] Wenkert,[43] and Jackson,[44] these biosynthetic transformations continue to present special challenges for synthetic chemists attempting to mechanistically emulate their molecular construction steps.

A direct Cope rearrangement[51] on open-chain L-Trp to access **1** is still missing. Herein we report, for the first time, a detailed study of an efficient [3,3]-Cope rearrangement (from C3 to C4), under biomimetic and environmentally friendly conditions (Scheme 1C). Additionally, a regio- and stereoselective [1,3]-rearrangement and an intermolecular prenyl transfer reaction resulting in pyrroloindolines (with C3-normal prenyl substitution) are reported. These reactions are appealing additions to the synthetic toolkit, considering the tediousness that prefunctionalization of the C4 position of indole demands for synthesizing complex, bioactive natural products.

RESULTS AND DISCUSSION

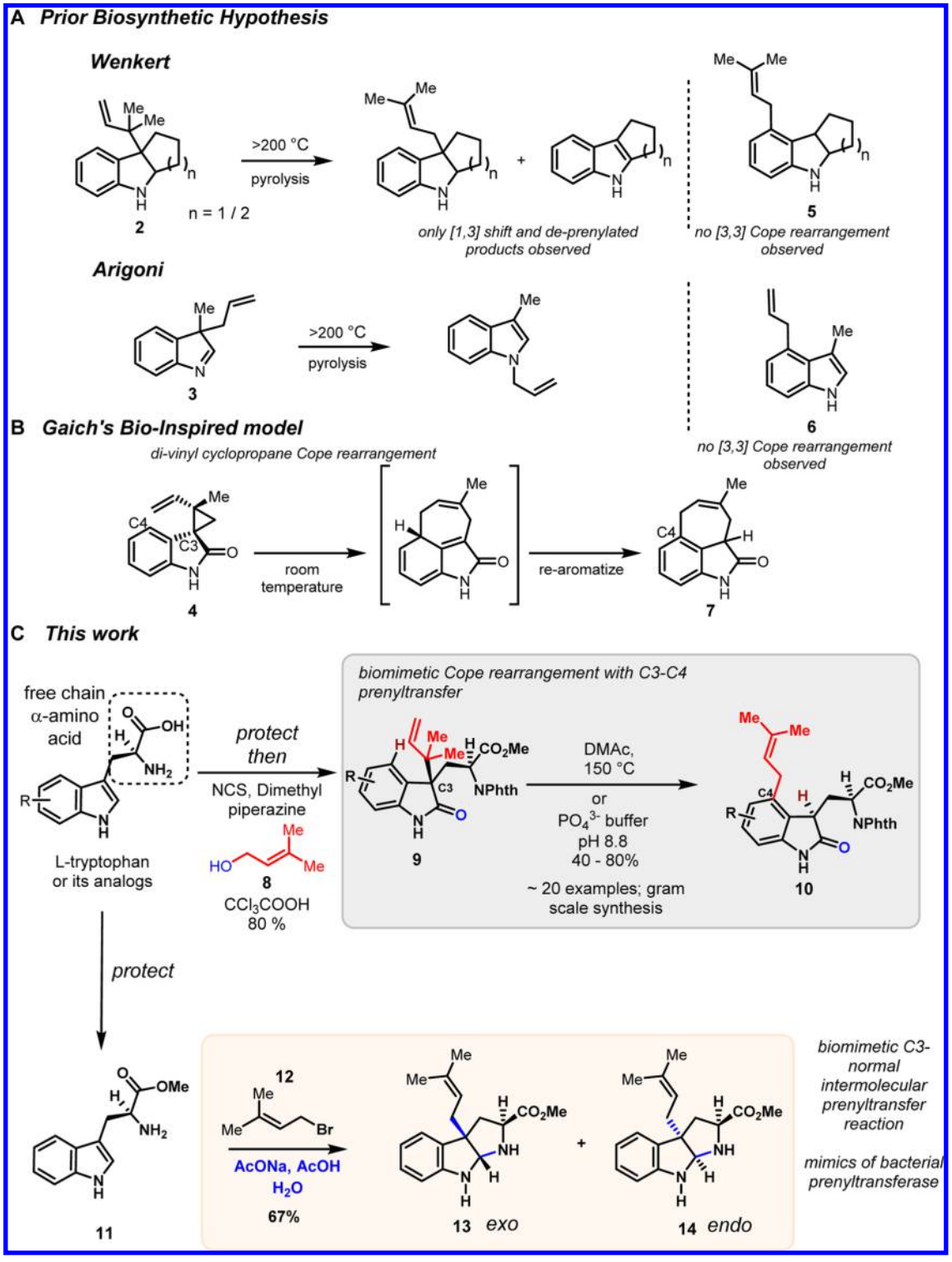
Access to Substrates for a [3,3]-Cope Rearrangement. As shown in Table 1, in order to test the feasibility of a [3,3]-sigmatropic rearrangement on the open-chain indole scaffold, we prepared a variety of substrates using a Meerwein–Eschenmoser–Claisen rearrangement[52−54] on C3-substituted indoles (**15**). Treatment of nitrile-containing C3-substituted indole **15a** with *N*-chlorosuccinimide (NCS) in the presence of 1,4-dimethylpiperazine, prenol (**8**), and trichloroacetic acid resulted in a 61% yield of oxindole **16a**. The series of reverse-prenylated oxindoles synthesized included *N*-phthalyl-protected tryptamine (**16b**), its *N*-Me-Tosyl protected variant (**16c**), substituted indole C3-propionic acid carboxyethyl ester (**16d**) and its methyl ketone version (**16e**), and a simpler C3-methyl substitution (**16f**). The series of other substituted C3-reverse prenylated oxindoles prepared for this study included examples **16g−k** possessing a C6-carboxymethyl ester substitution and a C6-fluoro-, C6-chloro-, C7-methyl-, and C5-methoxy-substituted oxindoles, respectively, all in moderate to high percent isolated yields. Technically, any allylic alcohol could participate in the one-step method involving activation with NCS as shown in eq 1, and therefore a series of nonprenyl alcohols were engaged to prepare oxindoles **16l−o**, respectively. The extended prenyl chain compounds geraniol and nerol gave oxindoles **16p,q**, respectively. Treatment of derivative **15r** with (*E*,*E*)-farnesol resulted in the formation of **16r**.

Heat- and Microwave-Promoted [3,3]- and [1,3]-Prenyl Transfer Rearrangements. Having synthesized **16a−r** as precursors for testing the [3,3]-sigmatropic rearrangement, we first attempted to identify the optimal set of solvent and temperature conditions to effect this transformation. A series of solvents ranging from those with very low dielectric constants such as toluene and decalin to highly polar solvents with very high dielectric constants such as dimethylacetamide (DMAc) and water were screened (see Table S3 in the Supporting Information). Bearing in mind that oxindole C3-substitution drastically affects the conformational preferences and populations with respect to reactivity at the C4 position,[55] we chose to test the feasibility of the [3,3]-sigmatropic rearrangement with a C3-methyl substituent for reasons of least perturbation to the process of the two olefins engaging in the rearrangement. Therefore, **16f** was subjected to thermal rearrangement conditions, it was observed that many solvents were suboptimal in effecting any rearrangement, and we recovered unreacted starting **16f**. Upon employing DMAc and decalin, two solvents with drastically different polarities, we observed a dramatic shift in the regioselectivity of rearrangement products, as illustrated in Scheme 2. When it was heated to 160 °C in DMAc, oxindole **16f** gave the Cope rearrangement product **17f** in 32% yield (see the Supporting Information for additional details).

When decalin was employed as the solvent, under reflux temperature, we observed smooth and near-quantitative conversion to C3-dimethylallyl oxindole **18f**, which contained a *normal* prenyl substitution. A formal [1,3]-prenyl transfer process at the C3 position of oxindole had occurred under

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

Scheme 1. (A) Prior 4-DMATS Enzymatic Mimics That Failed, (B) C3−C4 Divinyl Cyclopropane Ring-Opening Cope Rearrangement Reported by Schwarzer and Gaich,[48] and (C) Description of Intra- and Intermolecular Prenyl Transfer Reactions under Biomimetic Conditions Reported Herein



decalin as the nonpolar solvent. Thus, mechanistically divergent pathways were found to be operative under the two solvent conditions. Excited by the prospect of observing a [3,3]-sigmatropic (reverse-prenyl to prenyl) rearrangement occurring between the C3 and C4 positions of oxindole **16f**, we next tested a series of oxindoles for estimating the synthetic efficiency of the Cope rearrangement. As shown in Table 2 (eq 2), various substitution patterns were studied, including substituents at the C3, C5, C6, and C7 positions. Cyanoethyl-containing **16a** rearranged to give the [3,3]-product **17a** in 31% yield. The protected tryptamine **16b** underwent a [3,3]-sigmatropic shift to the C4 position in 74% yield. A range of substitution patterns was tested, and uniformly, the efficiency of the [3,3]-rearrangement was evaluated as given in Table 2.

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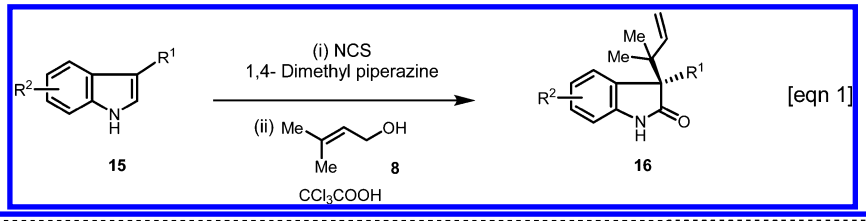
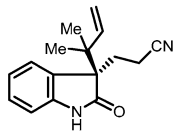
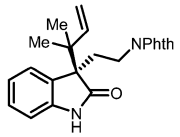
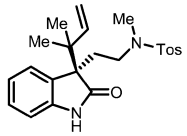
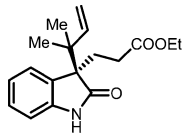
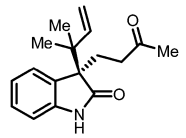
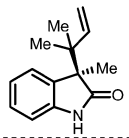
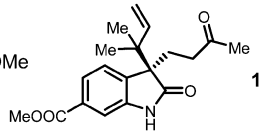
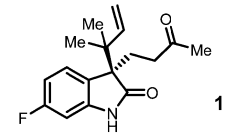
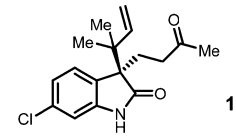
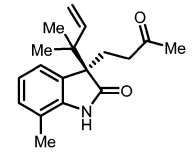
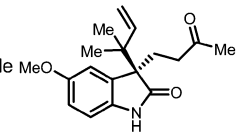
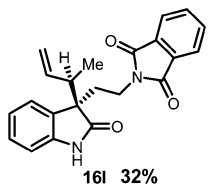
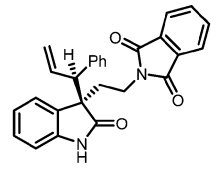
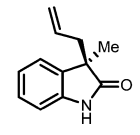
Table 1. Prenyl Transfer Reaction for Synthesis of Reverse-Prenylated Oxindoles

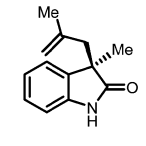


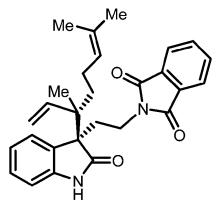
R1	R2	Product	#	% yield
CN	H		16a	61
NPhth	H		16b	61
Me N Tos	H		16c	66
COOEt	H		16d	55
O Me	H		16e	50
Me	H		16f	65
C6-COOMe			16g	74
C6-F			16h	52
C6-Cl			16i	40
C7-Me			16j	63
C5-OMe			16k	65

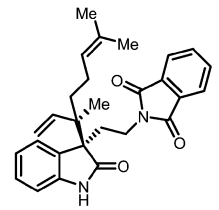

16l 32%

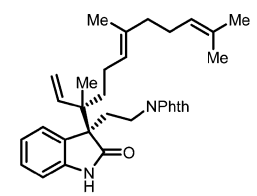

16m 47%


16n 47%


16o 53%


16p derived from geraniol 58%

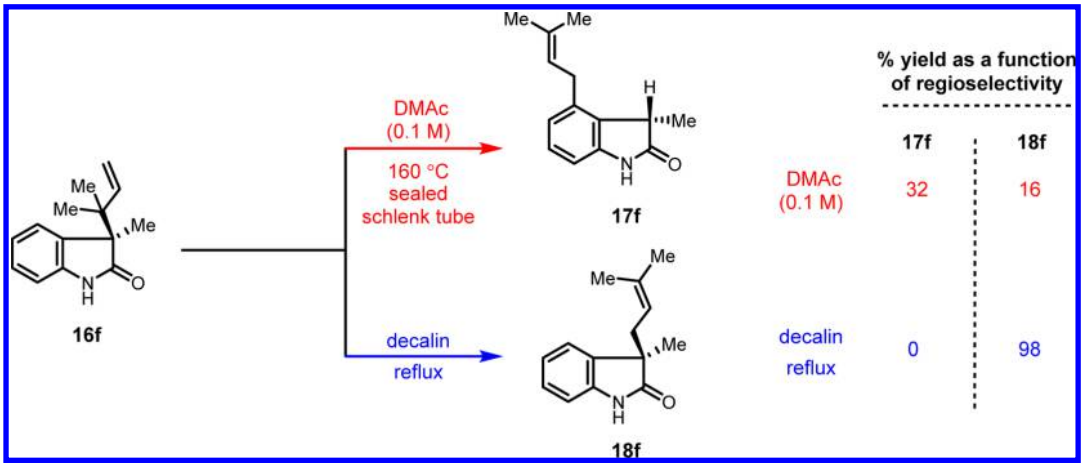

16q derived from nerol 60%


16r 48%

Minor amounts of [1,3]-rearrangement products were formed in some cases. We probed the probable involvement of a radical-mediated process during the formation of products resulting from a [1,3]-prenyl rearrangement. On the basis of similar studies performed by Harwood et al. on related Claisen rearrangements,[56−58] we wondered if the radical process initiated by atmospheric oxygen could then be can inhibited under presence of hydroquinone. Accordingly, when **16e,f** were

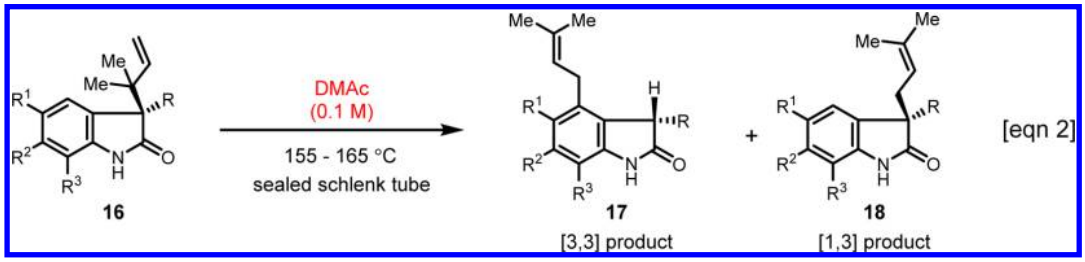
dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

Scheme 2. Shift of Regioselectivity for Prenyl Transfer Reactions with Drastically Different Solvent Dielectric Constants[a]



[a]% yield refers to isolated yield after chromatography.

Table 2. Substrate Scope and Generality Given as a Function of R Group Variability at the C3 Position of Oxindoles[a]



	substituents						yield (%)	
substrate	R	R^1	R^2	R^3	time (h)	conversion (%)	[3,3]-**17**	[1,3]-**18**
16a	CH_2CH_2CN	H	H	H	20	nd	31	<5
16b	CH_2CH_2NPhth	H	H	H	17	62	74	4
16c	$CH_2CH_2N(Tos)Me$	H	H	H	18	60	57	11[c]
16d[c]	CH_2CH_2COOEt	H	H	H	48	50	52	<5
16e	$CH_2CH_2COCH_3$	H	H	H	43	nd	43 (50[b])	ca. 10[c]
16f	Me	H	H	H	50	nd	32 (36[b])	16
16g[d]	$CH_2CH_2COCH_3$	H	COOMe	H	17	nd	43	<5
16h	$CH_2CH_2COCH_3$	H	F	H	15	ns	<5	<5
16i	$CH_2CH_2COCH_3$	H	Cl	H	15	ns	<5	<5
16j	$CH_2CH_2COCH_3$	H	H	Me	18	45	60	10[c]
16k	$CH_2CH_2COCH_3$	OMe	H	H	22	nd	45 (50[b])	<5
16s	$CH_2CH(NPhth)COOMe$	H	H	H	40	100	61	<5
16t	$CH_2CH_2N(Nos)Me$	H	H	H	15	58	50	11[c]

[a]Sterically larger R groups encouraged [3,3]-rearrangement. Abbreviations: nd, not determined; n, −not stable under the conditions tested. [b]Isolated yield based on recovered starting material. [c]Calculated from ^{1}H NMR data. [d]Unoptimized.

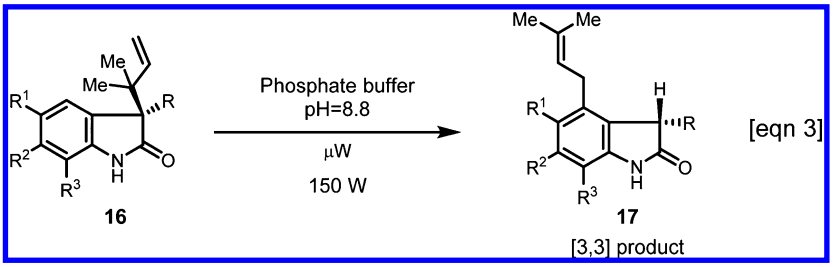
independently subjected to [1,3]-prenyl rearrangement conditions in decalin, we observed complete recovery of starting material, even after 72 h. However, the reaction proceeded well when hydroquinone was eliminated, suggesting that the radical-based mechanism was probable. Overall, in non-isatin-derived substrates (**16e**,**f**) as well as in isatin-derived cases (**21a**−**c**; vide infra), we observed a radical pathway to be operative under [1,3]-rearrangement processes.

The synthetic utility of examples **16b**, **c**, **s**, **t** is particularly noteworthy, as many alkaloid natural products possess a tryptamine or tryptophan side chain and their C4-prenylated products are directly accessed through this [3,3]-rearrangement process. Convinced that the strategy was working on oxindoles with the tryptamine side chain, we studied the conditions to improve reaction rates and yields. Multiple boron- and aluminum-based Lewis acids failed to catalyze the Cope rearrangement process. However, heating the oxindole in aqueous phosphate buffer with microwave assistance dramatically accelerated the rearrangement (Table 3).

For example, the cyanoethyl oxindole **16a**, when subjected to microwave irradiation at 150 W and 150 °C, in just 60 min (as opposed to several hours under nonmicrowave heating conditions) gave a 58% yield of the C4-prenylated **17a**. Phthalyl-protected tryptamine gave a 75% yield of the C4-prenylated product **17b** in 40 min. Substrates **16c**−**t** all underwent a [3,3]-Cope rearrangement in durations that ranged between 40 and 90 min, at pH 8.8 in phosphate buffer. Except in cases **16f**, **h**, **k** all other substrates gave the [3,3]-rearranged product **17** as the major product under these conditions. The three exceptions produced minor amounts of

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

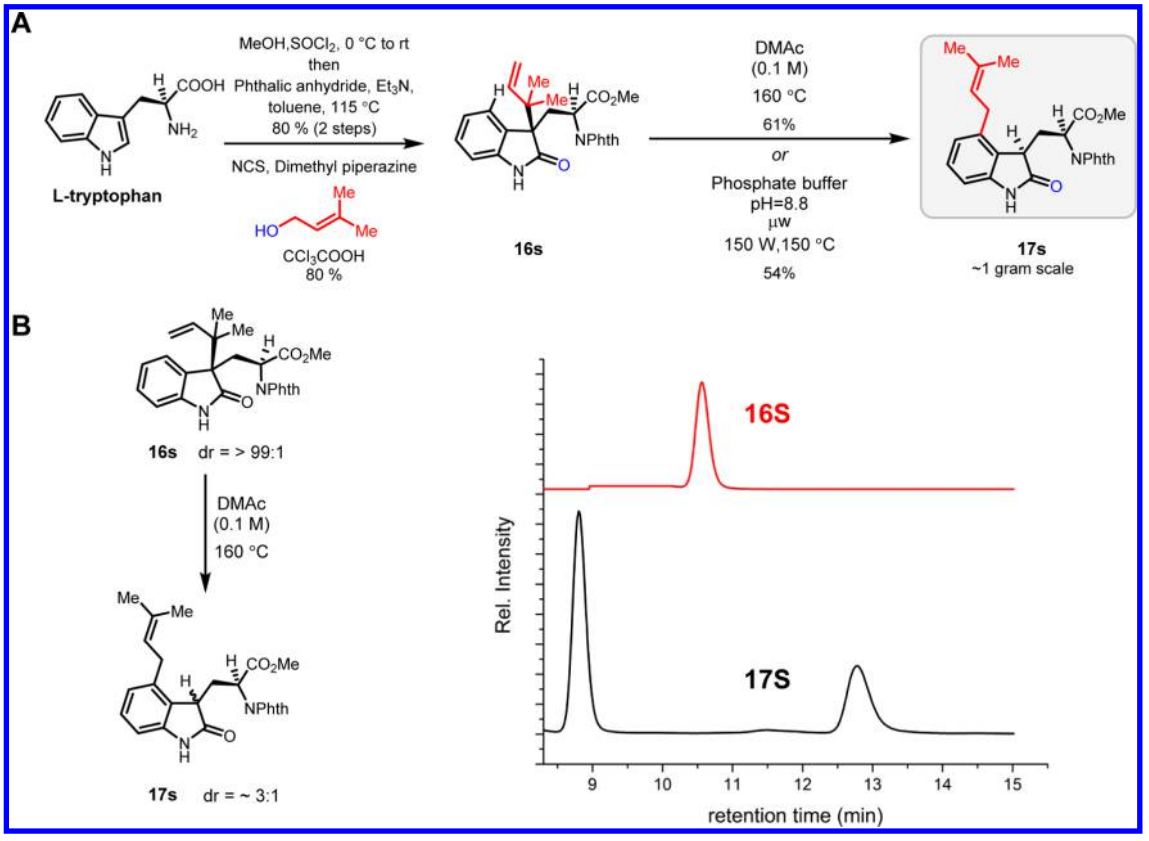
Table 3. C4-Prenylation of Tryptophan Scaffold under Phosphate-Buffered Conditions[a]



substrate	substituent R	R^1	R^2	R^3	temp (°C)	time (min)	yield [3,3]-product **17** (isolated) (%)
16a	CH_2CH_2CN	H	H	H	150	60	58
16b	CH_2CH_2NPhth	H	H	H	150	40	75
16c	$CH_2CH_2N(Tos)Me$	H	H	H	150	65	40
16d	CH_2CH_2COOEt	H	H	H	150	65	42
16e	$CH_2CH_2COCH_3$	H	H	H	150	70	46
16f	Me	H	H	H	165	90	16[b]
16g	$CH_2CH_2COCH_3$	H	COOMe	H	150	60	40
16h	$CH_2CH_2COCH_3$	H	F	H	150	60	40[d]
16i	$CH_2CH_2COCH_3$	H	Cl	H	150	60	45
16j	$CH_2CH_2COCH_3$	H	H	Me	150	62	50
16k	$CH_2CH_2COCH_3$	OMe	H	H	150	70	48[c]
16s	CH_2 CH(NPhth)COOMe	H	H	H	150	60	54
16t	$CH_2CH_2N(Nos)Me$	H	H	H	150	50	ns

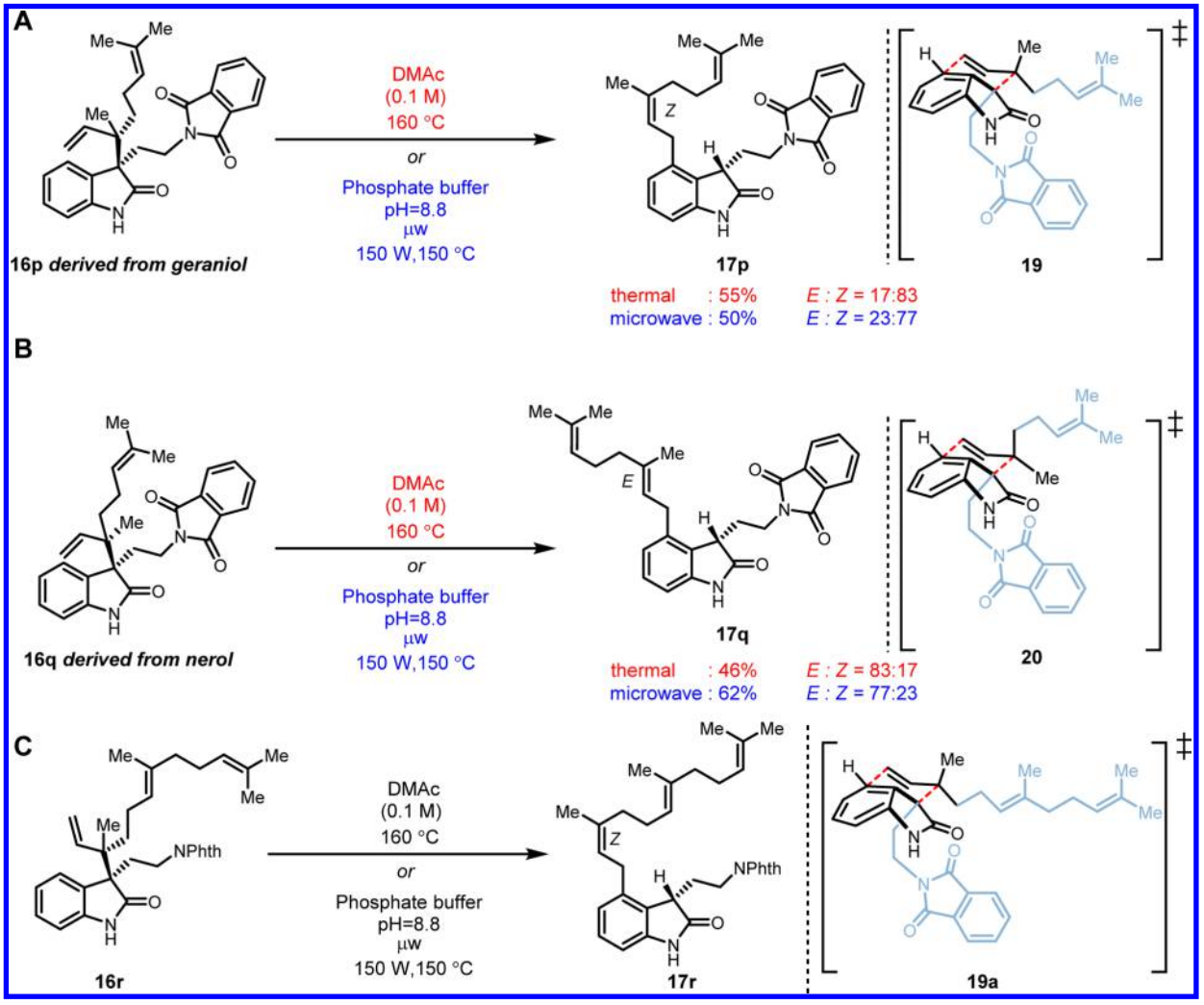
[a]Abbreviations: ns, not stable under conditions tested. [b]42% of [1,3]-product was obtained [c]13% of [3,3]-product without an R group was obtained. [d]22% of [1,3]-product was obtained.

Scheme 3. (A) [3,3]-Prenyl Transfer reaction on L-Trp-Derived 16s, Starting with C3-Reverse Prenylation Followed by DMAc or Phosphate-Buffer-Mediated Rearrangement To Yield 17s and (B) Chiral HPLC Analysis of a Single Diastereomer of 16s Converting to a 3:1 Mixture of Diastereomers of 17s



dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

Scheme 4. [3,3]-Prenyl Transfer Reaction on α-Amino Acid, Starting with C3-Reverse Prenylation To Yield 16s after Protection Followed by Heat- or Microwave-Mediated Rearrangement, (A) [3,3]-Cope Rearrangement of Geraniol-Derived 16p, (B) [3,3]-Cope Rearrangement of Nerol-Derived 16q, and (C) [3,3] Cope Rearrangement of (*E*,*E*)-Farnesol-Derived 16r



either a [1,3]-prenyl rearrangement product (like in Table 2) for **16f**,**k** or showed loss of the C3-substituent altogether in the case of **16h**.

Realizing that a worthy test of a Cope rearrangement to construct a C4-prenylated indole scaffold will be on a α-amino acid scaffold of L-Trp, as shown in Scheme 3A, we attempted sequential prenylation on the amino acid L-Trp upon protection (as its methyl ester *N*-phthalyl counterpart) by subjecting it to a Meerwein−Eschenmoser−Claisen rearrangement with prenol, resulting in **16s** in 80% yield. Thus, on subjecting **16s** to either the thermal rearrangement condition in DMAc or microwave irradiation in phosphate buffer at pH 8.8, we were glad to observe formation of **17s** in 58−61% and 54% yields, respectively. The product **17s** was formed as a 1:1 mixture of diastereomers (Scheme 3A).

This observation prompted that the Cope rearrangement/tautomerization sequence of C3-reverse prenylation substrates **16** to products **17** is not necessarily stereospecific. In order to further test the stereoselective nature of this transformation, we sought to explore a control experiment wherein L-Trp-derived **16s**, purified to a single diastereomeric composition (dr: >99:1), could be subjected to the Cope rearrangement/tautomerization sequence and the product stereochemistry be evaluated. Scheme 3B illustrates the results of such an experiment. Upon chiral HPLC analysis of the product **17s**, we clearly observed a 3:1 ratio of products varying likely at the C3 stereocenter. As the likelihood of epimerization at the α-carbon of the α-amino acid chain is low, we attribute this result to the presence of either antipode at the C3 center. Overall, this Cope rearrangement proved to be stereoselective with respect to the C3 oxindole center, and its stereochemical course could also be translated to linear isoprenoid containing oxindoles.

As shown in Scheme 4, a chain-elongated version of the prenyl transfer process was next tested on substrate **16p**. Similar to the case for **16s**, oxindole **16p** was accessed, as a single diastereomer (in 58% yield), through a Meerwein−Eschenmoser--Claisen rearrangement on *N*-phthalyl tryptamine (Table 1). Subjecting **16p** to a [3,3]-Cope rearrangement process in DMAc solvent at 160 °C gave a 17:83 mixture (in 55% yield) of *E* and *Z* geometric isomers that differed in their newly formed double-bond geometry. Similarly, when **16p** was subjected to microwave irradiation conditions, **17p** was obtained as a 23:77 mixture of *E* and *Z* isomers, as shown in Scheme 4B. A Zimmerman−Traxler-like transition state assembly, depicted by **19**, probably rationalizes the observation of formation of the *Z* isomer as the major product, keeping in

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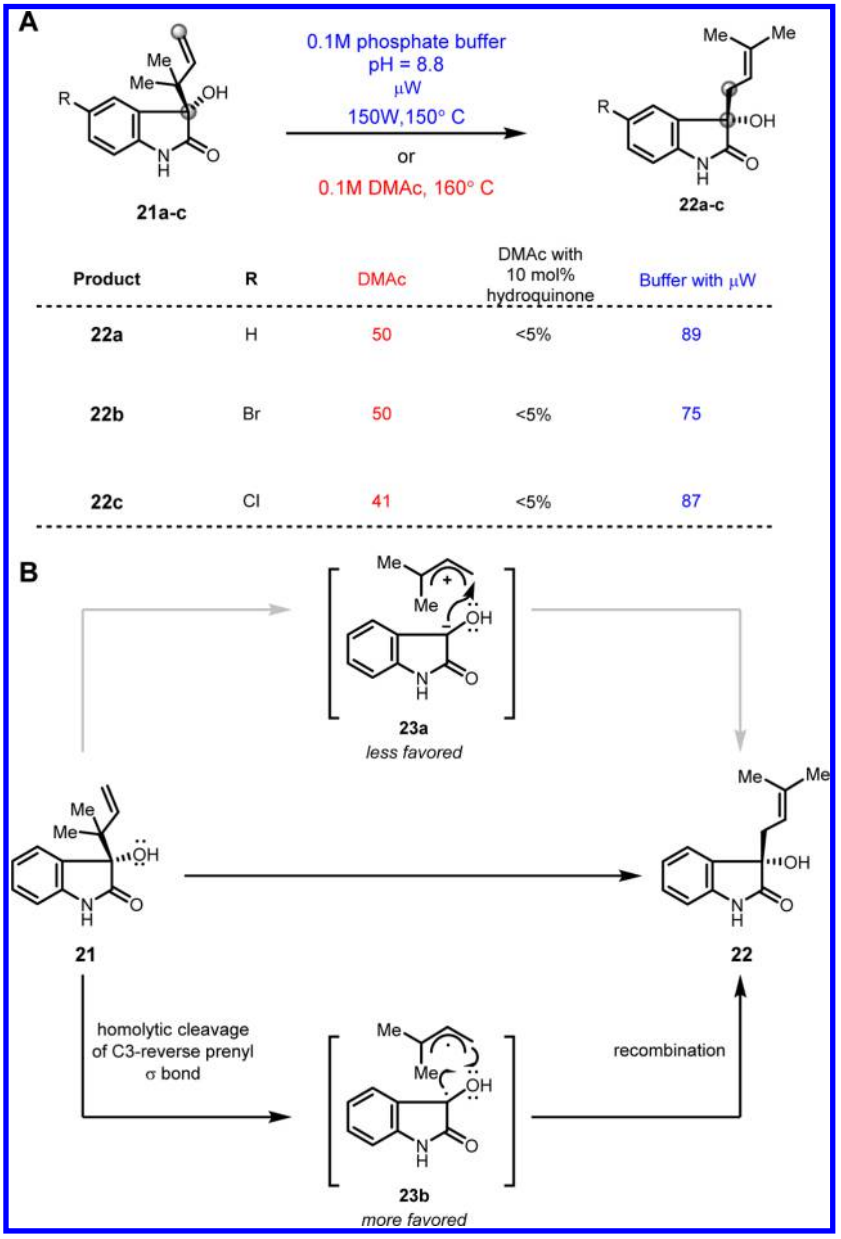
Scheme 5. (A) [1,3]-Prenyl Transfer Reaction for C3-Hydroxy-Substituted Oxindoles and (B) Proposed Pathway with Radical Intermediate 23b Likely To Explain Regioselectivity Observed for Formation of 22 Based on Hydroquinone Inhibition Data in A



Product	R	DMAc	DMAc with 10 mol% hydroquinone	Buffer with μW
22a	H	50	<5%	89
22b	Br	50	<5%	75
22c	Cl	41	<5%	87

mind that the participating atoms of the oxindole portion are sp^2 hybridized. The oxindole **16q**, on the other hand, was obtained as an 8:1 mixture of diastereomers (in 60% yield) from the Meerwein−Eschenmoser−Claisen rearrangement on *N*-phthalyl tryptamine and nerol as the allylic alcohol (Table 1).

When **16q** was subjected to the Cope rearrangement process, the C3 to C4 prenyl migration occurred smoothly, resulting in **17q**, which possessed the *E* geometry across the newly formed olefin in 46% and 62% yields, under DMAc or phosphate-buffered conditions with microwave irradiation, respectively. The product displayed the geometric ratio of *E* and *Z* isomers reflective of a situation similar to **17p** but opposite in magnitude due to the nature of the diastereomeric composition of **16q**. Overall, we observed stereospecific C3 to C4 prenyl transfer migration under Cope rearrangement conditions, with respect to the olefinic portion of the isoprenoid chain, for **16p,q**. Similarly, when oxindole **16r** (previously synthesized from (*E,E*)-farnesol in 48% yield) was subjected to Cope rearrangement conditions, **17r** was obtained in 52% yield as a single isomer containing the *Z,E* double-bond geometry. Thus, we see complete conservation of the double-bond geometry related from farnesol substrate to product **17r** after two pericyclic rearrangements.

Mechanistic Evaluation of [3,3]-Cope Rearrangement. Scheme 5 outlines the results we observed when C3-hydroxy oxindoles **21a−c** were subjected to the Cope rearrangement conditions. Interestingly, as opposed to other examples where anionic oxy-Cope rearrangements are known to occur in a more accelerated manner, we observed no [3,3]-rearrangement in any of these examples. Instead, every substrate underwent a nearly exclusive [1,3]-prenyl rearrangement resulting in C3-*normal* prenyl substitution in **22a−c**. The synthetic efficiency of these thermally activated [1,3]-prenyl migration processes was reasonable, and **22a−c** were obtained in 50%, 50%, and 41%

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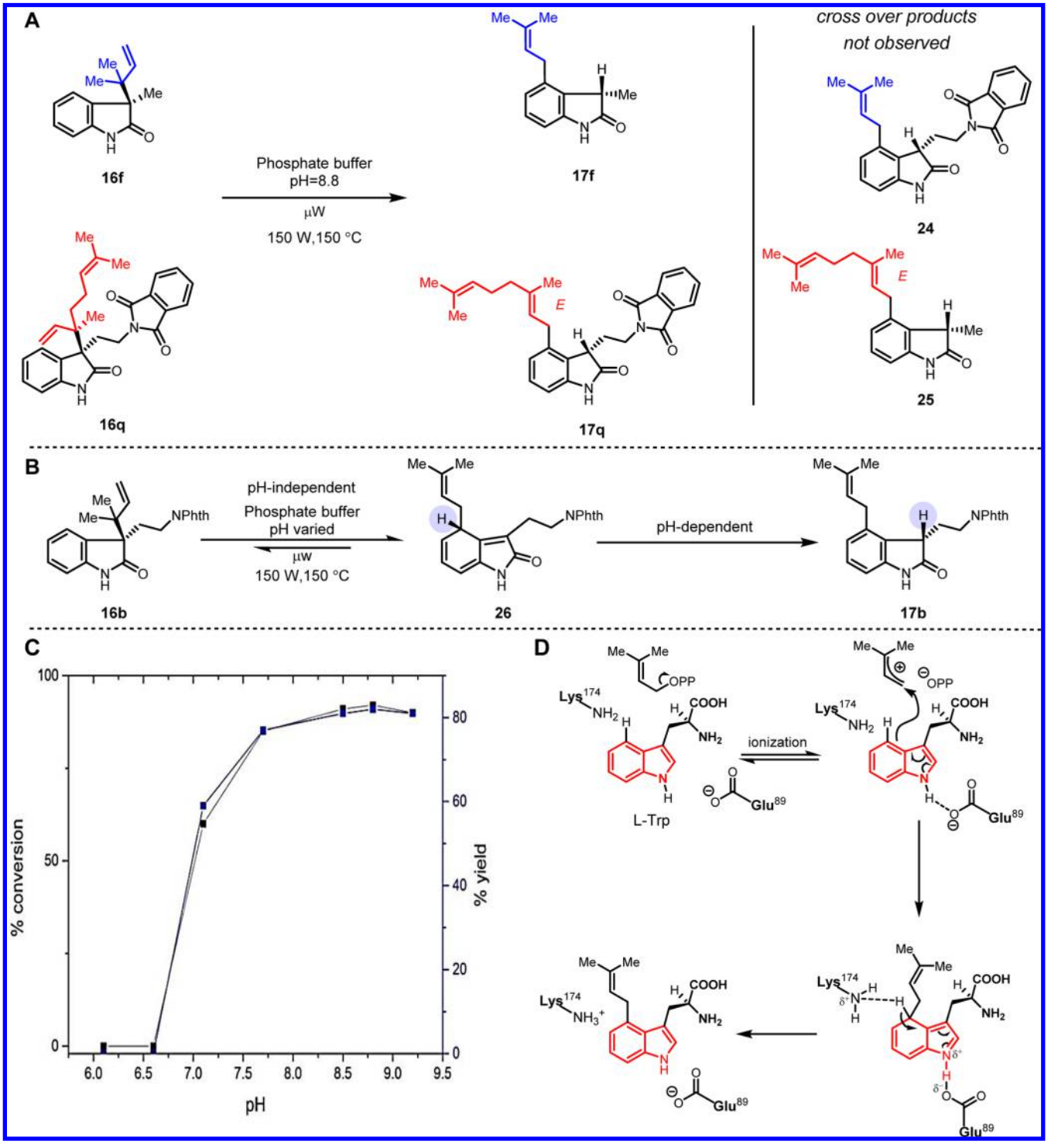
Scheme 6. Mechanism of [3,3]-Prenyl Transfer Reaction: (A) Crossover Experiment; (B) Two-Step Mechanism; (C) pH Dependence of (B); (D) Electrophilic Aromatic Substitution Model of 4-DMATS Involving Deprotonation of C4-Hydrogen Similar to Intermediate 26



yields, respectively, with DMAc as the solvent. The corresponding efficiency for [1,3]-prenyl transfer under microwave-mediated conditions were considerably higher at 89%, 75%, and 87%, respectively, for **22a**–**c**. While the [3,3]-Cope rearrangement process was investigated mechanistically as discussed below, the 3-hydroxy examples provided a reasonable rationale, as represented in Scheme 5B, for their mechanism for the [1,3]-prenyl migration event. Similar to the case for **16e**,**f**, the presence of 10 mol % hydroquinone during the [1,3]-prenyl migration event entirely abrogated the formation of **22a**–**c**. On the basis of nature's biosynthetic repertoire involving C_5 (and higher order) isoprenoid pyrophosphates (DMAPP, GPP, FPP, etc.) in numerous examples of chain elongation and branching events, it is reasonable to consider a prenyl cation involvement (as shown in **23a**) for the transformation of **21** to **22**. However, considering the fact that a radical inhibitor causes complete

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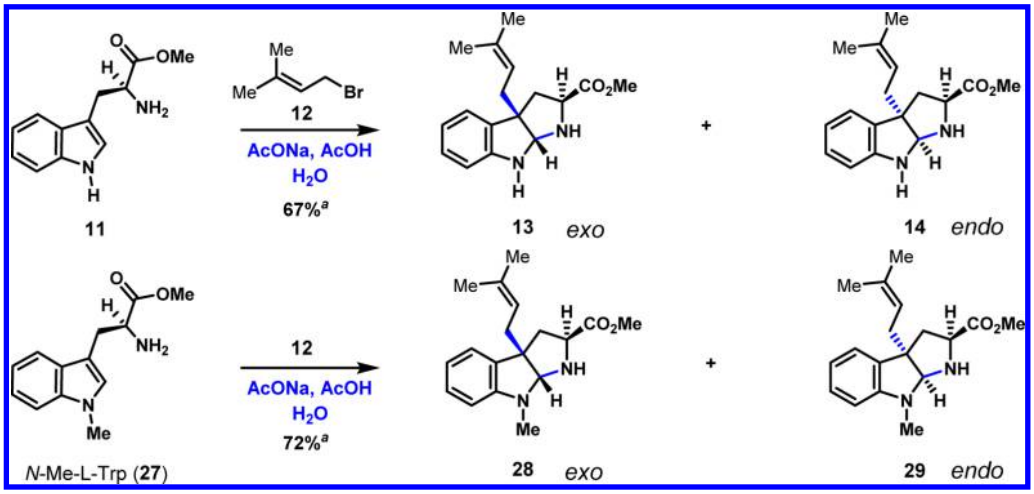
Scheme 7. Intermolecular Prenyl Transfer Reaction To Construct a Pyrroloindoline Skeleton under Biomimetic Conditions



shutdown of the conversion, we propose that a radical-based pathway involving the tightly coupled radical pair **23b** as the likely intermediate toward **22**. Wenkert and Sliwa, in their reported study[43] on 6-5-6 (or 6-5-5) pyrroloindolines that were C3-reverse prenylated, observed this type of a [1,3]-prenyl shift consistently for most examples they attempted under pyrolysis conditions. The mechanistic explanation offered here also could be applied to examples seen in their studies.

We next probed the [3,3]-Cope process for a mechanistic understanding, specifically asking whether the process is strictly intramolecular or if there was any intermolecularity involved when the prenyl group migrates from the C3 to the C4 position of the oxindole ring system. Therefore, as shown in Scheme 6A, a competition experiment was conducted with **16f**, **q** premixed in an equimolar ratio and were subjected to phosphate-buffered solution at pH 8.8 and microwave irradiation at 150 °C. At complete conversion of the starting materials, we observed *only* the formation of **17f,q**. The product containing a prenyl (C_5) group on the C4 position of tryptamine scaffold represented by **24** and the product containing a geranyl (C_{10}) unit at the C4 position of methyl-carrying oxindole represented by **25** were not observed by ^{1}H NMR. This observation confirmed that an intermolecular scrambling of prenyl groups was not operative. No prenyl-scrambled [1,3]-products were seen either, indicating overall that the Cope process is intramolecular under these conditions.

Biochemical characterizations of DMATS and FgaPT2 revealed the presence of Lys174 and Glu89 as crucially important and essential residues.[3,37−39] Their roles were clarified through mutation studies, which revealed that Glu89 was involved in activation of the indole nucleophile through engagement in hydrogen bonding and ensuing removal of the N1 hydrogen. Lys174, whose site-directed mutagenesis nearly abolished the production of **1**, served as the base responsible for deprotonation and tautomerization of the intermediate formed immediately after the C4-alkylation.

In our studies, as represented in Scheme 6B, considering that a [3,3] rearrangement results in the nonaromatic intermediate **26** (equivalent to the biological case preceding formation of **1**), we wondered if this formal two-step process leading to C4-prenylated **17b** would be sensitive to varying pH. Due to the fact that this "rearomatization" is essential for formation of the eventual product **17**, the influence of a basic or acidic medium (mimicking the presence or absence of Lys174) is expected to accelerate or decelerate the overall process, if this rearomatization event is rate-limiting. Therefore, we conducted an investigation by estimating the percent conversion (and corresponding percent yield) of the C4-prenylated product (**17b**) formation, starting from **16b** at various pHs in phosphate-buffered solutions (Scheme 6C). Between pH 6 and 6.5, there was no **17b** observed, indicating that the deprotonation of the C4 proton to cause rearomatization was shut down in even a slightly acidic medium. Drastic change toward >60% conversion and yield was observed at pH ≥7.0. The conversion and yield improved consistently with increase in pH and were maximized close to pH 8.8. From a biomimetic standpoint this result was a near replica of the enzyme active site. The first step of the two-step process, a [3,3]-Cope rearrangement, is not expected to involve polar or ionic transition states (though this is not unprecedented) and therefore is expected to be pH neutral. Though we treat this Cope rearrangement as an equilibrium process, we do expect the apparent equilibrium constant to be favoring **26**, considering steric congestion at C3 of the precursor oxindole **16**. Therefore, the presence of a basic medium (at pH 8.8) is seen to dramatically shift the overall efficiency toward **17b** through expediting the proton transfer event, resulting in a fully aromatic and stabilized **17b**. With **17b** as a representative, we anticipate most other substrates undergoing this prenyl transfer process to conform to this biomimetic pH effect.

The Cope rearrangement was also found to be sensitive to the ring substituent and the steric composition at the C3 position. As shown in Figure S1 (Supporting Information), the duration of the thermal rearrangement for each substitution pattern revealed the effect that the individual substitutions had on the transformation. Electron-withdrawing substituents on the aromatic ring of oxindole (**16i, g, h**) promoted the rate of the prenyl transfer process to the C4 position. This correlated with the expectation that the formal second step of the process involving tautomerization of intermediate **26** is expected to be promoted by electron-withdrawing substituents by virtue of lowering the pK_a of the proton at the C4 position of **26** (see the blue highlight in Scheme 6B). Conversely, the presence of an electron-donating methoxy substituent (**16k**) slowed down the rearrangement process, again by virtue of increasing the pK_a of the proton at the C4 position of **26**. The presence of substituents on the C3 chain of the tryptamine or tryptophan scaffold to a general extent had a positive effect on promoting

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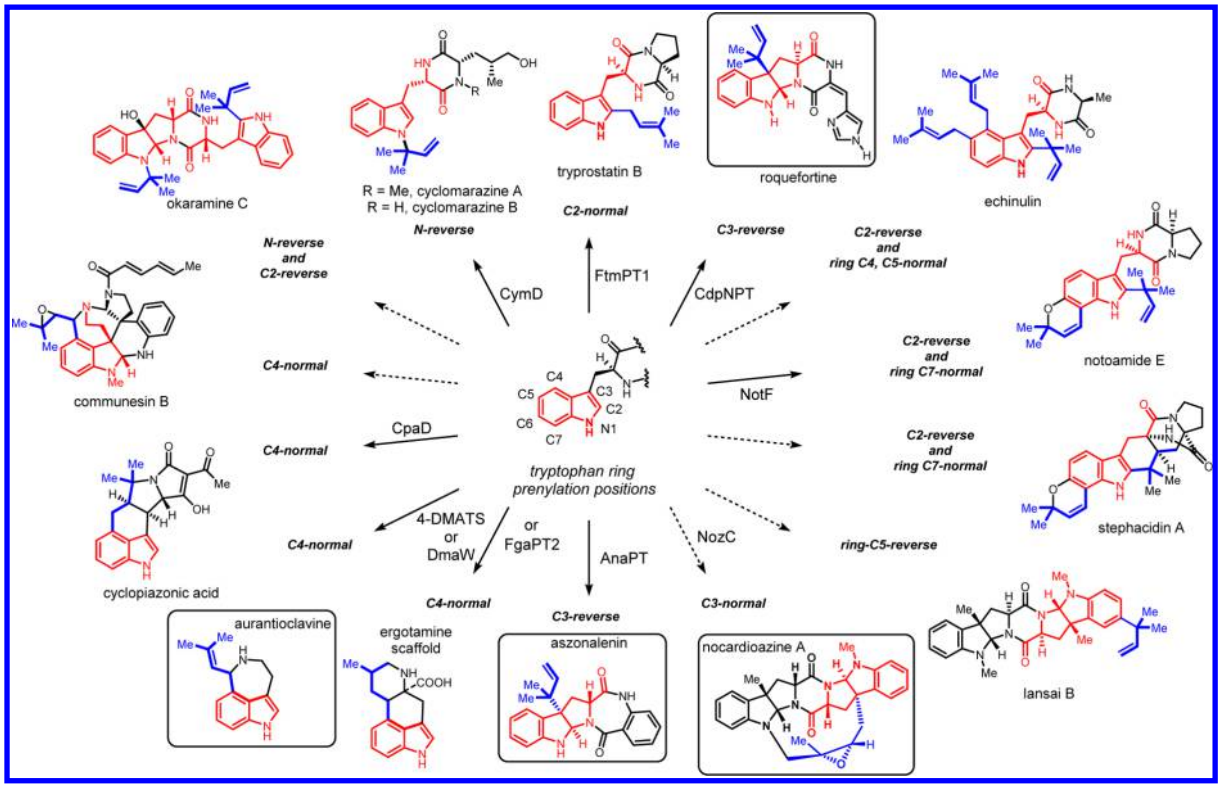

Figure 2. Indole prenyltransferases and their regioselectivity of prenylation (blue) on L-Trp (red). Bold arrows reflect the fact that the indicated enzyme has been biochemically characterized. Scaffolds presented in boxes represent examples for which biomimetic pathways are presented in this report.

the rate of the rearrangement process. Steric effects were manifested in two specific ways. The first type of steric effect that was observed was on examples that carried a C3 substituent. Among a cyanoethyl group (**16a**), an ethyl methyl ketone (**16e**), an ethyl carboxy ester (**16d**), and a protected tryptophan (**16s**), we found that the rate was influenced by a subtly balancing steric factor that tilted toward faster rearrangement for substituents that were too bulky. Second, a possible Thorpe−Ingold effect was apparent for substituents that forced the reactive olefins to engage in the rearrangement process. An extreme of this correlation can be seen in Gaich's reports that carry a cyclopropane to promote the rearrangement.[48] Additionally, the absence of a Cope rearrangement on any of the nonreverse prenyl oxindole examples (**16l−o**) corroborated the apparent presence of the Thorpe−Ingold effect imposed by the presence of the geminal dimethyl substitution of the reverse-prenyl group. The relatively slow and sluggish rate observed for C3-methyl substitution (**16f**) was attributable to a similar effect.

Prenylating the C3 position of indoles directly with alkyl electrophiles is a challenging process under aqueous conditions. To address this challenge, an intermolecular prenyl transfer reaction was attempted next, as outlined in Scheme 7. L-Trp methyl ester (**11**) was subjected to prenylation at the C3 position in the presence of prenyl bromide in sodium acetate−acetic acid buffer and pH 2.7 at room temperature and gave rise to products **13** and **14** in a 4:1 ratio favoring the *exo* product. The corresponding N1-methylated substrate (**27**) underwent the C3-prenylation event with prenyl bromide and resulted in a mixture of *exo* and *endo* diastereomers **28** and **29**. The use of prenyl bromide to activate the C3 position of the indole ring system concomitantly resulted in formation of the pyrroloindoline ring system. Both in the case of nonmethylated **13** and in the case of methylated **29**,the products were characterized for their relative stereochemistry through measurement of the NOESY correlations around the protons of the pyrroloindoline skeleton. The prenylation of indoles under aqueous conditions is challenging. We derived our inspirations from the report of Bocchi et al., though we fortuitously arrived at drastic improvements over the percent yields of the pyrroloindoline products.[59] Additionally, the indole C3-prenylation conditions we report herein results in approaches to natural product biosynthetic studies of the nocardioazine alkaloids. A high degree of biomimeticity is evident between our prenylation strategy (**11** to **13** + **14**; and **27** to **28** + **29**) and those of the indole prenyltransferases observed in the literature leading to multiple alkaloid pathways encoded by the *Aspergillus* sp.[21] and the *Bacillus subtilis* ComX pheromonone synthesizing ComQ geranyl transferase enzyme.[60,61]

Tryptophan Prenylations in Biosynthesis. Tryptophan prenylation (with C_5 isoprenoid) is a well-documented enzymatic phenomenon. Every possible site for enzymatic prenylation on the indole scaffold (N1−C7) has been observed, with the individual enzyme being functionally active on select prenylation position(s) (Figure 2). Among the individual pathways, indole prenyltransferases arguably are one of the most intricate enzymes involved in the biosynthesis of complex natural products. Fungal biosynthetic pathways leading to a large collection of prenylated indole alkaloids (a few representative examples are presented in Figure 2) have spurred an extensive body of work on their structure elucidation, asymmetric synthesis, medicinal chemistry, and related studies. Gene clusters and their characterization have evolved in the postgenomic era and have actively inspired

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

further chemoenzymatic syntheses, mechanistic enzymology,[7,8,13,14,62] and structural biology of these unique biocatalysts.[63] For example, aurantioclavines are representative of the synthetic challenges that continue to spur newer methodologies to emerge.[64,65] Well into the 21st century, the only known L-Trp prenyltransferase was from *Claviceps purpurea*. Genome sequencing projects on *Aspergillus* spurred the identification of a series of indole prenyltransferases that were found to prenylate a variety of substrates such as L-Trp, diketopiperazines containing tryptophan units, and L-Trp-conjugated benzodiazepines. As summarized in Figure 2, a spectrum of prenylation patterns can now be observed. Specifically, the work presented herein mimics the indole prenyltransferases operative toward the biosynthesis of four specific alkaloid classes. The C3-reverse prenylation reactions used herein for the synthesis of a series of oxindoles **16** mimic the products seen from AnaPT-catalyzed C3-reverse prenylation, leading to the formation of aszonalenin and CdpNPT-catalyzed formation of roquefortines. The C3−C4 prenyl migrating Cope rearrangement reported herein for the series of compounds **16** transforming to **17** mimics the catalytic action carried out by mutant FgaPT2. The product resulting from the Cope rearrangement is identical with that formed from a direct alkylation seen in *Claviceps purpurea* DMATS. The mimicry shown by the intramolecular [1,3]-prenyl migration event (**16** to **18** or **21** to **22**) results in products that share structural similarity to C3-*normal* prenylating enzymes. The intermolecular prenylation reaction resulting in the C3-*normal* pattern shown in Scheme 6 also mimics these indole prenyltransferases. One such pathway leads to the formation of nocardioazines, biosynthesized by *Nocardiopsis* sp. CMB M0232. Ongoing activity in our laboratory is currently elucidating the enzyme action of NozC, a bacterial homologue that prenylates C3 positions of L-Trp diketopiperazine substrates.

Interestingly, the catalysis affected by indole prenyltransferases is now beginning to be better understood through X-ray crystallography. As represented in those with known three-dimensional structures show remarkable similarity in their biophysical folds leading to overlapping substrate−product relationships with surprising levels of promiscuity. Overall, this work is anticipated to enrich the synthetic toolkit[63] and add novel directions for future investigations in alkaloid total synthesis and biosynthesis. Moreover, in conjunction with earlier work published by Schwarzer et al.,[48,49] these reactions together offer feasibility for a Cope rearrangement mechanism, at least under nonenzymatic conditions. In a related manner, a possible extension of this work could be directly applicable to the synthesis of compounds that may throw light on the mechanisms of FgaPT2 and DMAW synthase enzymes from *Aspergillus* and *Claviceps*, respectively.

CONCLUSION

L-Trp presents a dazzling array of nucleophilic positions that enzymes take full advantage of by prenylating various positions in natural product biosynthetic pathways. Synthetic mimicry of these selective biocatalysts has been rare, primarily due to the challenge in taming regio- and stereoselectivities of such transformations. Herein we present a facile [3,3]-prenyl group migrating Cope rearrangement that was evaluated for its synthetic efficiency, substituent diversity, biomimeticity, and possible mechanistic underpinnings. We find that the phosphate-buffered microwave-mediated conditions uniformly resulted in good yields of C4-prenylated products. Mechanistically, pH variations and the ensuing sensitivity revealed a slower step involving tautomerization of the C4 proton to the C3 position. In turn, this implied that the Cope rearrangement itself could be the reversible faster step. Parallel to the Cope rearrangement, we found that use of a nonpolar solvent such as decalin promoted a regioselective [1,3]-prenyl transfer reaction resulting in C3-*normal* prenyl substituted oxindoles. C3-hydroxylation also enforced a stricter selectivity for the [1,3]-prenyl transfer process. Direct prenylation of the L-Trp scaffold was also effected under biomimetic conditions, resulting in pyrroloindolines with C3-*normal* prenyl substitution. Overall, these conditions are expected to find use in natural product total synthesis, considering the urgent need for stereoselective methods for complex alkaloid construction. The design and synthesis of mechanistic probes for DMATS and related enzymes may also be possible through these prenyl transfer reactions. These results may prompt synthetic chemists in the alkaloid field to explore additional methods of elaborating the indole ring utilizing prenylations and sigmatropic rearrangements.

EXPERIMENTAL SECTION

Representative Procedures. *General Procedure A: Reverse Prenylation of C3-Substituted Indoles.* A two-neck round-bottomed flask with a magnetic stir bar (capped with septa) was dried under vacuum. Once cooled to ambient temperature under inert atmosphere, the flask was charged with 3-cyanoethylindole (**15a**; 256 mg, 1.5 mmol) that was mixed with 5 mL of dry dichloromethane and stirred. Freshly distilled 1,4-dimethylpiperazine (0.13 mL, 0.96 mmol) was added, and the reaction flask was cooled to 0 °C on ice. Recrystallized NCS (221 mg, 1.65 mmol) was added, and the stirring continued at the same temperature for 2 h under nitrogen. In a separate round-bottomed flask, CCl_3COOH (60 mg, 0.36 mmol) and prenyl alcohol (0.3 mL, 3.0 mmol) were mixed, diluted with dichloromethane (2 mL), and stirred at room temperature. After 2 min, this mixture was cannulated into the reaction flask at 0 °C and the ensuing mixture was gradually warmed to room temperature and stirred for 12 h. Wet dichloromethane (3 mL with 5 drops of water) was added dropwise to the mixture to quench the reaction. The reaction mixture was washed with 0.5 M $NaHCO_3$ (20 mL), 0.5 M HCl (20 mL), and brine (20 mL). The organic layers were dried with anhydrous Na_2SO_4 and evaporated to yield the product mixture as a yellow oil. The mixture was subjected to silica gel chromatography (18% ethyl acetate in hexanes) to yield the purified product **16a** (as a representative example) in 61% isolated yield (236 mg, 0.93 mmol) as a pale oil that solidified upon standing.

General Procedure B: Cope Rearrangement under Thermal Conditions. The C3 reverse-prenylated oxindole **16s** (1.0 g, 2.31 mmol) was taken in a vial and capped with a septum. Under nitrogen, **16s** was dissolved in DMAc to form a 0.1 M solution. The solution was transferred to a Schlenk tube using a syringe and capped under nitrogen and heated in an oil bath at 155 °C for 40 h. The reaction mixture was cooled to room temperature, and DMAc was removed in vacuo. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with brine (15 mL × 3). The organic layer was dried with anhydrous Na_2SO_4 and evaporated to give the crude product, which was subjected to silica gel chromatography (refer to general experimental details in the Supporting Information) with ca. 1/4 v/v ethyl acetate/hexane as eluent, and the product oxindole **17s** (as a representative example) was isolated as a pale yellow solid in 61% yield (610 mg, 1.41 mmol).

General Procedure C: Cope Rearrangement under Microwave Irradiation. A 10 mM phosphate buffer (pH 8.8) was prepared by dissolving 3 mg of monosodium phosphate hydrate and 262 mg of disodium hydrogen phosphate in 100 mL of doubly deionized water. C3-reverse prenylated oxindole (30 mg, 0.08 mmol) **16b** was dissolved in 0.75 mL of buffer in a microwave-compatible sealed tube and subjected to irradiation of 150 W of 150 °C over 40 min. The reaction

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

mass was extracted with ethyl acetate (10 mL) and washed with brine (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated to give the crude reaction mixture, which upon purification by preparative TLC (refer to general experimental detailsin the Supporting Information) gave the product **17b** in 75% yield (22.5 mg, 0.06 mmol).

General Procedure D: [1,3]-Prenyl Group Rearrangement. The C3 reverse-prenylated oxindole (50 mg, 0.13 mmol) **16b** was transferred to a Schlenk tube as a dichloromethane solution. The solvent was removed by purging nitrogen followed by high vacuum to remove the last traces of dichloromethane. The oxindole was added to decalin to form a 0.1 M solution (turbidity observed). The Schlenk tube was sealed and heated in an oil bath at 185 °C for 2 days. Decalin was evaporated in vacuo. The crude sample was directly loaded into the silica gel column using toluene as solvent. The product **18b** was obtained in 65% yield (32.5 mg, 0.087 mmol) after column chromatography with 1/4 v/v ethyl acetate/hexane.

General Procedure E: Intermolecular C3-Prenylation of Tryptophan. To a magnetically stirred solution of L-Trp methyl ester **11** (400 mg, 1.83 mmol) in sodium acetate/acetic acid buffer (pH 2.7, 30 mL) was added prenyl bromide (635 μL, 5.50 mmol) over a period for 45−50 min at room temperature. The resulting mixture was stirred at the same temperature overnight. Evaporation of acetic acid under reduced pressure resulted in a solid residue which was dissolved in ethyl acetate. The solution was neutralized by addition of sodium carbonate solution, and the ester was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, giving a diastereomeric mixture of the cyclic products **13** and **14** (in a 4/1 ratio) in 67% overall yield (358 mg, 1.25 mmol) (based on recovered starting material).

*C3-Reverse Prenylated Oxindole Substrates. 3-(3-(2-Methylbut-3-en-2-yl)-2-oxoindolin-3-yl) propanenitrile (**16a**).* Following the general procedure A, treatment of 3-cyanoethylindole **15a** gave product **16a** (236 mg, 0.93 mmol) as a white solid (mp 86 °C) in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (br s, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 7.16 (m, 1H), 7.03 (td, *J* = 7.6, 0.8 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.03 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.13 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.02 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.47 (ddd, *J* = 13.6, 11.2, 5.6 Hz, 1H), 2.17 (ddd, *J* = 13.6, 11.2, 4.8 Hz, 1H), 1.91 (ddd, *J* = 16.8, 11.2, 5.6 Hz, 1H), 1.71 (ddd, *J* = 16.4, 11.2, 4.8 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 142.6, 141.9, 128.8, 128.5, 125.6, 122.1, 119.1, 114.5, 110.1, 58.1, 42.1, 27.7, 22.1, 21.9, 13.4. FT-IR (KBr, ν_{max}): 3275, 2923, 1737, 1620, 1491, 1370 cm^{-1}. HRMS (EI): calcd for $C_{16}H_{18}N_2O$ $[M]^+$ 254.1419, found 254.1415.

*N,4-Dimethyl-N-(2-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-ethyl)benzenesulfonamide (**16c**).* Following the general procedure A, treatment of *N*-Me-Tos-ethylindole (500 mg, 1.52 mmol) **15c** gave product **16c** as a pale yellow solid (mp 104 °C), in 66% yield (414 mg, 1.01 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (br s, 1H) 7.46−7.41 (m, 2H), 7.26−7.18 (m, 4H), 7.05 (td, *J* = 7.6, 1.2 Hz, 1H), 6.85−6.82 (m, 1H), 6.01 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.96 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.6 (s, 3H), 2.59−2.51 (m, 1H), 2.43 (ddd, *J* = 13.4, 10.2, 5.2 Hz, 1H), 2.37 (s, 3H), 2.32 (ddd, *J* = 13.2, 10.3, 5.9 Hz, 1H), 2.06 (ddd, *J* = 13.4, 10.3, 4.8 Hz, 1H), 1.1 (s, 3H), 1.0 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 143.2, 143.1, 141.5, 134.4, 129.7, 129.6 (2 × C), 128.2, 127.4 (2 × C), 126.0, 121.9, 114.0, 109.4, 56.7, 47.1, 42.1, 35.3, 29.5, 22.2, 21.8, 21.6. FT-IR (KBr, ν_{max}): 2923, 1737, 1620, 1491 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{28}N_2O_3S$ $[M]^+$ 412.1821, found 412.1818.

*Ethyl 3-(3-(2-Methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**16d**).* Following the general procedure A, treatment of 3-ethyl-carboxyethylindole (281 mg, 1.29 mmol) **15d** gave product **16d** as a colorless oil, in 55% yield (214 mg, 0.71 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.23- 7.14 (m, 2H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.86−6.82(m, 1H), 6.05 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.1 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.0 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.98 (qq, *J* = 10.8, 7.2 Hz, 2H), 2.37 (ddd, *J* = 13.6, 11.1, 5.2 Hz, 1H), 2.2 (ddd, *J* = 13.6, 11.6, 4.8 Hz, 1H), 1.96 (ddd, *J* = 16.4, 11.6, 5.2 Hz, 1H), 1.62 (ddd, *J* = 17.2, 11.6, 4.8 Hz, 1H), 1.17 (s, 3H), 1.14(t, *J* = 7.2 Hz, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.1, 173.2, 143.2, 141.8, 130.1, 128.2, 125.9, 121.8, 114.0, 109.3, 60.5, 58.2, 42.0, 30.1, 26.5, 22.4, 21.9, 14.2. FT-IR (KBr, ν_{max}): 3275, 2956, 1713, 1620, 1491, 1148 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_3$ $[M]^+$ 301.1678, found 301.1677.

*3-(2-Methylbut-3-en-2-yl)-3-(3-oxobutyl)indolin-2-one (**16e**).* Following the general procedure A, treatment of 3-(2-oxobutyl)indole (450 mg, 2.41 mmol) **15e** gave product **16e** as a semisolid (mp 98 °C) in 50% yield (324 mg, 1.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.15−7.12 (m, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89−6.85 (m, 1H), 6.03 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.99 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.31−2.07 (m, 3H), 1.91 (s, 3H), 1.70−1.63 (m, 1H), 1.16 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 181.6, 143.2, 141.8, 130.4, 128.1, 125.9, 121.9, 113.9, 109.6, 58.1, 41.9, 39.1, 30.1, 25.2, 22.5, 21.9. FT-IR (KBr, ν_{max}): 2923, 1713, 1620, 1462, 1370, 752 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1572, found 271.1580.

*Methyl 3-(2-Methylbut-3-en-2-yl)-2-oxo-3-(3-oxobutyl)indoline-6-carboxylate (**16g**).* Following the general procedure A, treatment of 6-carboxymethyl-3-(2-oxobutyl)indole (411 mg, 1.67 mmol) **15g** gave product **16g** as a pale yellow oil in 74% yield (407 mg, 1.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (br s, 1H), 7.68 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 5.98 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.05 (dd, *J* = 10.8, 0.8 Hz, 1H), 4.94 (dd, *J* = 17.4, 0.8 Hz, 1H), 3.89 (s, 3H), 2.37−2.02 (m, 3H), 1.89 (s, 3H), 1.71−1.54 (m, 1H), 1.15 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 181.1, 166.7, 142.6, 142.2, 135.8, 130.2, 125.5, 123.4, 114.3, 110.2, 58.3, 52.4, 42.1, 38.9, 29.9, 25.0, 22.4, 21.8. FT-IR (KBr, ν_{max}): 3259, 2957, 1716, 1628, 1458, 1286 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{23}NO_4$ $[M]^+$ 329.1627, found 329.1626.

*6-Fluoro-3-(2-methylbut-3-en-2-yl)-3-(3-oxobutyl)indolin-2-one (**16h**).* Following the general procedure A, treatment of 6-carboxymethyl-3-(2-oxobutyl)indole (453 mg, 2.20 mmol) **15h** gave product **16h** as a pale yellow oil in 52% yield (331 mg, 1.15 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 7.10−6.98 (m, 1H), 6.71−6.60 (m, 2H), 5.99 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.06 (dd, *J* = 10.8, 1.1 Hz, 1H), 4.96 (dd, *J* = 17.4, 1.1 Hz, 1H), 2.32−2.01 (m, 3H), 1.91 (s, 3H), 1.76−1.63 (m, 1H), 1.14 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 182.0, 163.9, 161.5, 143.2, 142.9, 126.8, 125.6, 114.2, 108.3, 98.3, 57.8, 42.0, 39.0, 30.0, 25.2, 22.4. FT-IR (KBr, ν_{max}): 3262, 2968, 1709, 1600, 1488, 1206 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{20}FNO_2$ $[M]^+$ 289.1478, found 289.1473.

*6-Chloro-3-(2-methylbut-3-en-2-yl)-3-(3-oxobutyl)indolin-2-one (**16i**).* Following the general procedure A, treatment of 6-chloro-3-(2-oxobutyl)indole (291 mg, 1.31 mmol) **15i** gave product **16i** as a pale yellow solid (mp 114 °C) in 40% yield (160 mg, 0.53 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (br s, 1H), 7.05 (dd, *J* = 8.3, 3.7 Hz, 1H), 7.00−6.88 (m, 2H), 5.99 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.0 Hz, 1H), 4.97 (dd, *J* = 17.4, 1.0 Hz, 1H), 2.34−2.02 (m, 3H), 1.93 (s, 3H), 1.75−1.63 (m, 1H), 1.16 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 181.5, 142.9, 142.7, 133.8, 128.8, 126.6, 121.8, 114.4, 110.2, 57.9, 42.1, 39.0, 30.1, 25.1, 22.5, 21.9. FT-IR (KBr, ν_{max}): 3262, 2968, 1709, 1600, 1488, 1206 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{20}ClNO_2$ $[M]^+$ 305.1183, found 305.1185.

*7-Methyl-3-(2-methylbut-3-en-2-yl)-3-(3-oxobutyl) indolin-2-one (**16j**).* Following the general procedure A, treatment of 7-methyl-3-(2-oxobutyl)indole (291 mg, 1.45 mmol) **15j** gave product **16j** as a pale yellow oil in 63% yield (259 mg, 0.91 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (br s, 1H), 7.02 (m, 1H), 6.95 (d, *J* = 6.9 Hz, 1H), 6.92−6.83 (m, 1H), 6.02 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.03 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.96 (dd, *J* = 17.4, 1.2 Hz, 1H), 2.31 (s, 3H), 2.29−2.23 (m, 1H), 2.21−2.02 (m, 2H), 1.88 (s, 3H), 1.69 (ddd, *J* = 15.6, 11.3, 3.4 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 182.3, 143.3, 140.7, 129.9, 129.4, 123.1, 121.7, 118.9, 113.7, 58.4, 41.8, 39.1, 30.0, 25.2, 22.5, 21.8, 16.6. FT-IR (KBr, ν_{max}): 3262, 2968, 1709, 1713, 1600, 1488, 1206 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_2$ $[M]^+$ 285.1729, found 285.1722.

*5-Methoxy-3-(2-methylbut-3-en-2-yl)-3-(3-oxobutyl)indolin-2-one (**16k**).* Following the general procedure A, treatment of 5-

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

methoxy-3-(2-oxobutyl)indole (455 mg, 2.09 mmol) **15k** gave product **16k** as a white solid (mp 136 °C) in 65% yield (410 mg, 1.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (br s, 1H), 6.85−6.77 (m, 1H), 6.76−6.68 (m, 2H), 6.05 (dd, J = 17.4, 10.8 Hz, 1H), 5.07 (dd, J = 10.8, 1.2 Hz, 1H), 4.97 (dd, J = 17.4, 1.2 Hz, 1H), 3.75 (s, 3H), 2.31−2.18 (m, 1H), 2.17−2.01 (m, 2H), 1.90 (s, 3H), 1.77−1.63 (m, 1H), 1.16 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 181.4, 155.1, 143.1, 135.2, 131.9, 114.0, 113.1, 112.3, 109.7, 58.5, 55.7, 41.9, 39.1, 30.0, 25.2, 22.4, 21.8. FT-IR (KBr, ν_{max}): 3262, 2968, 1709, 1713, 1600, 1488, 1206 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_3$ $[M]^+$ 301.1678, found 301.1674.

*2-(2-(3-(But-3-en-2-yl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (**16l**).* Following the general procedure A, treatment of *N*-phthalyltryptamine (400 mg, 1.38 mmol) **15l** gave product **16l** as a mixture of major and minor diastereomers (dr = 5.6:1) as a pale yellow oil in 32% yield (159 mg, 0.44 mmol) (alongside full recovery of unreacted starting material). Data for the major diastereomer are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (br s, 1H), 7.71−7.66 (m, 2H), 7.64−7.58 (m, 2H), 7.11−7.05 (m, 1H), 7.01−6.98 (m, 1H), 6.87 6.74 (m, 2H), 5.83 (ddd, J = 16.9, 10.3, 9.0 Hz, 1H), 5.20−5.09 (m, 2H), 3.57−3.48 (m, 2H), 2.71 2.67 (m, 1H), 2.55−2.43 (m, 1H), 2.23 2.18 (m, 1H), 0.73 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.1, 168.0 (2 × C), 141.5, 138.0, 133.8 (2 × C), 132.0 (2 × C), 129.6, 127.9, 124.2, 123.0 (2 × C), 122.2, 117.6, 110.1, 54.9, 45.5, 34.4, 33.6, 14.8. FT-IR (KBr, ν_{max}): 3257, 3065, 2972, 2927, 1772, 1707, 1619, 1469, 720 cm^{-1}. HRMS (EI): calcd for $C_{22}H_{20}N_2O_3$ $[M]^+$ 360.1474, found 360.1469.

*2-(2-(2-Oxo-3-(1-phenylallyl)indolin-3-yl)ethyl)isoindoline-1,3-dione (**16m**).* Following the general procedure A, treatment of *N*-phthalyltryptamine (400 mg, 1.38 mmol) **15m** gave product **16m** as a mixture of major and minor diastereomers (dr = 8:1) as a pale yellow oil in 47% yield (274 mg, 0.65 mmol). Data for the major diastereomer are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.72 7.56 (m, 4H), 7.30 (d, J = 7.4 Hz, 1H), 7.06 6.90 (m, 4H), 6.85 (t, J = 7.5 Hz, 1H), 6.67 (d, J = 7.2 Hz, 2H), 6.59 (d, J = 7.6 Hz, 1H), 6.25 (dt, J = 16.3, 10.3 Hz, 1H), 5.35−5.19 (m, 2H), 3.69 (d, J = 10.0 Hz, 1H), 3.48 (t, J = 6.6 Hz, 2H), 2.63 (dt, J = 14.6, 7.4 Hz, 1H), 2.38−2.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 168.0 (2 × C), 141.6, 138.4, 135.4, 133.8 (2 × C), 132.0 (2 × C), 129.1, 128.4 (2 × C), 128.3, 127.8 (2 × C), 127.0, 124.3, 123.1 (2 × C), 122.1, 119.2, 110.1, 58.0, 55.9, 34.4, 33.3. FT-IR (KBr, ν_{max}): 3420, 2926, 2855, 1716, 1470, 1265 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{22}N_2O_3$ $[M]^+$ 422.1630, found 422.1626.

*3-Allyl-3-methylindolin-2-one (**16n**).* Following the general procedure A, treatment of C3-methylindole (260 mg, 1.98 mmol) **15n** gave product **16n** as a pale yellow oil in 47% yield (174 mg, 0.93 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (br s, 1H), 7.23−7.14 (m, 2H), 7.03 (td, J = 7.5, 1.0 Hz, 1H), 6.95−6.91 (m, 1H), 5.51 (ddt, J = 17.1, 10.1, 7.3 Hz, 1H), 5.08−4.98 (m, 1H), 4.97 4.92 (m, 1H), 2.64−2.44 (m, 2H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.1, 140.5, 134.2, 132.6, 127.9, 123.3, 122.4, 118.9, 109.9, 48.9, 42.5, 22.9. FT-IR (KBr, ν_{max}): 3371, 2253, 1709, 1470, 1160 cm^{-1}. HRMS (EI): calcd for $C_{12}H_{13}NO$ $[M]^+$ 187.0997, found 187.0998.

*3-Methyl-3-(2-methylallyl)indolin-2-one (**16o**).* Following the general procedure A, treatment of C3-methylindole (500 mg, 3.82 mmol) **15o** gave product **16o** as a pale yellow oil in 53% yield (406 mg, 2.02 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.23−7.16 (m, 2H), 7.07−7.00 (m, 1H), 6.92−6.84 (m, 1H), 4.61 4.59 (m, 1H), 4.56 4.53 (m, 1H), 2.73 (dd, J = 13.5, 0.8 Hz, 1H), 2.49 (d, J = 13.5 Hz, 1H), 1.41 (s, 3H), 1.39 (dd, J = 1.4, 0.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 141.3, 140.4, 134.3, 127.8, 123.7, 122.4, 114.5, 109.8, 49.3, 45.7, 25.1, 23.8. FT-IR (KBr, ν_{max}): 3214, 2971, 2925, 1708, 1621, 1473, 1232 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{15}NO$ $[M]^+$ 201.1154, found 201.1155.

*2-(2-(3-(3,7-Dimethylocta-1,6-dien-3-yl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (**16p**).* Following the general procedure A, treatment of *N*-phthalyltryptamine (616 mg, 2.12 mmol) **15p** gave product **16p** as a single diastereomer (dr > 19:1) as a pale yellow oil in 58% yield (544 mg, 1.23 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.74−7.66 (m, 2H), 7.66−7.59 (m, 2H), 7.18 (d, J = 7.0 Hz, 1H), 7.03 (td, J = 8.0, 1.2 Hz, 1H), 6.86−6.76 (m, 2H), 5.82 (dd, J = 17.5, 10.9 Hz, 1H), 5.24 (dd, J = 10.9 and 1.1 Hz, 1H), 5.01 (dd, J = 17.5, 1.1 Hz, 1H), 4.94−4.84 (m, 1H), 3.42−3.21 (m, 2H), 2.48−2.32 (m, 2H), 1.82−1.64 (m, 2H), 1.57 (s, 3H), 1.46 (s, 3H), 1.35 (ddd, J = 19.3, 12.9, 6.5 Hz, 1H), 1.27−1.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 168.0 (2 × C), 141.7, 141.5, 133.8 (2 × C), 132.1 (2 × C), 131.4, 130.0, 127.9, 125.9, 124.6, 123.1 (2 × C), 121.7, 116.4, 109.7, 57.7, 45.8, 34.8, 34.4, 29.5, 25.8, 23.1, 17.7, 15.5. FT-IR (KBr, ν_{max}): 3319, 2923, 2253, 1773, 1712, 1620, 1475, 1402, 908, 733 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{30}N_2O_3$ $[M]^+$ 442.2256, found 442.2259.

*2-(2-(3-(3,7-Dimethylocta-1,6-dien-3-yl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (**16q**).* Following the general procedure A, treatment of *N*-phthalyltryptamine (475 mg, 1.64 mmol) **15q** gave product **16q** as a mixture of major and minor diastereomers (dr = 8:1) as a pale yellow oil in 60% yield (434 mg, 0.98 mmol). Data for the major diastereomer are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (br s, 1H), 7.71−7.64 (m, 2H), 7.63−7.56 (m, 2H), 7.18−7.13 (m, 1H), 6.98 (td, J = 7.7, 1.2 Hz, 1H), 6.85−6.79 (m, 1H), 6.75 (td, J = 7.6, 1.1 Hz, 1H), 6.01 (dd, J = 17.5, 10.8 Hz, 1H), 5.27−5.14 (m, 1H), 5.01−4.90 (m, 2H), 3.46−3.22 (m, 2H), 2.52−2.34 (m, 2H), 1.75−1.62 (m, 2H), 1.57 (s, 3H), 1.51−1.41 (m, 5H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 168.0 (2 × C), 142.0, 141.1, 133.7 (2 × C), 132.0 (2 × C), 131.3, 130.0, 127.9, 125.9, 124.7, 123.0 (2 × C), 121.5, 115.9, 109.8, 58.00, 46.0, 34.8, 34.0, 29.4, 25.8, 22.9, 17.7, 16.5. FT-IR (KBr, ν_{max}): 3428, 2923, 2354, 1713, 1563, 1462, 1370 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{30}N_2O_3$ $[M]^+$ 442.2256, found 442.2252.

*(E)-2-(2-(2-oxo-3-(3,7,11-trimethyldodeca-1,6,10-trien-3-yl)-indolin-3-yl)ethyl)isoindoline-1,3-dione (**16r**).* Following the general procedure A, treatment of *N*-phthalyltryptamine (900 mg, 3.10 mmol) **15r** gave product **16r** as a single diastereomer (dr > 19:1) as a pale yellow oil in 48% yield (760 mg, 1.49 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 7.72−7.66 (m, 2H), 7.66−7.59 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.03 (td, J = 7.7, 1.2 Hz, 1H), 6.88−6.76 (m, 2H), 5.84 (dd, J = 17.5, 10.9 Hz, 1H), 5.24 (dd, J = 10.9, 1.1 Hz, 1H), 5.05−4.97 (m, 2H), 4.91−4.87 (m, 1H), 3.46−3.21 (m, 2H), 2.50−2.29 (m, 2H), 2.01−1.97 (m, 2H), 1.86−1.83 (m, 1H), 1.82−1.71 (m, 1H), 1.70−1.60 (m, 4H), 1.54 (s, 3H), 1.46 (s, 3H), 1.43−1.33 (m, 1H), 1.32−1.18 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 168.0 (2 × C), 141.9, 141.5, 134.9, 133.8 (2 × C), 132.1 (2 × C), 131.4, 130.0, 127.9, 125.8, 124.5, 124.4, 123.1 (2 × C), 121.7, 116.4, 109.9, 57.7, 45.8, 39.7, 34.7, 34.4, 29.5, 26.7, 25.8, 23.0, 17.8, 16.1, 15.6. FT-IR (KBr, ν_{max}): 3358, 2974, 2891, 2362, 1777, 1714, 1624, 1563, 1479, 1406, 1370, 1047 cm^{-1}. HRMS (EI): calcd for $C_{33}H_{38}N_2O_3$ $[M]^+$ 510.2882, found 510.2880.

*Methyl-2-(1,3-Dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**16s**).* Following the general procedure A, treatment of *N*-phthalyl-L-tryptophan carboxymethyl ester (12.5 g, 0.035 mol) **15s** gave product **16s** as a pale yellow solid (mp 120 °C) in 80% yield (12.4 g, 0.029 mol) as a 1:1 mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.85−7.79 (m, 2H), 7.72 (br s, 1H), 7.67−7.61 (m, 2H), 7.60−7.51 (m, 4H), 7.33−7.24 (m, 2H), 7.09 (td, J = 7.6, 1.2 Hz, 1H), 6.87 (dd, J = 16.5, 7.6 Hz, 2H), 6.48 (d, J = 4.0 Hz, 2H), 6.26 (dt, J = 7.4, 4.4 Hz, 1H), 6.07 (t, J = 11.2 Hz, 1H), 6.02 (t, J = 11.2 Hz, 1H), 5.13 (dd, J = 7.4, 1.1 Hz, 1H), 5.10 (dd, J = 7.4, 1.1 Hz, 1H), 5.03 (dd, J = 15.1, 1.1 Hz, 1H), 4.98 (dd, J = 15.1, 1.1 Hz, 1H), 4.79 (dd, J = 10.3, 4.6 Hz, 1H), 4.25 (dd, J = 11.1, 2.1 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.21 (ABX, J = 14.8, 11.1 Hz, 1H), 3.05−2.95 (m, 2H), 2.90 (ABX, J = 14.8, 2.2 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 179.6, 169.8, 169.4, 167.4 (2 × C), 167.0 (2 × C), 142.9, 142.7, 142.1, 141.2, 134.1 (2 × C), 133.7 (2 × C), 131.8 (2 × C), 131.6 (2 × C), 130.1, 129.1, 128.7, 127.1, 125.9, 124.9, 123.6 (2 × C), 122.9 (2 × C), 122.0, 121.2, 114.4, 114.4, 110.0, 109.7, 56.9, 56.7, 53.1 (2 × C), 49.5, 49.1, 42.7, 42.4, 30.3, 28.9, 22.5, 22.1, 21.9, 21.5. FT-IR (KBr, ν_{max}): 2923, 1737, 1713, 1620, 1462, 1370 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{24}N_2O_5$ $[M]^+$ 432.1685, found 432.1666. HPLC: t_R for single diastereomer 10.8 min (Chiralpak AS column, 30% ^{i}PrOH/Hex). The assignments for proton NMR data are provided in Table S1 (Supporting Information).

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

*C4-Prenylated Products of Cope Rearrangement. 3-(4-(3-Methylbut-2-en-1-yl)-2-oxoindolin-3-yl)propanenitrile (**17a**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (53 mg, 0.21 mmol) **16a** gave product **17a** in 31% yield (16.4 mg, 0.06 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (7.5 mg, 0.029 mmol) **16a** gave product **17a** in 58% yield (4.4 mg, 0.017 mmol) as a colorless solid (mp 120 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (br s, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 5.21 (dddd, J = 6.9, 5.5, 2.8, 1.4 Hz, 1H), 3.62 (dd, J = 8.2, 3.1 Hz, 1H), 3.42−3.23 (m, 2H), 2.59−2.43 (m, 2H), 2.41−2.31 (m, 1H), 2.25−2.14 (m, 1H), 1.77 (d, J = 1.3 Hz, 3H), 1.75 (d, J = 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 141.6, 138.9, 134.1, 129.0, 124.8, 123.8, 121.4, 119.1, 108.1, 44.1, 31.5, 25.8, 25.6, 18.2, 13.4. FT-IR (KBr, ν_{max}): 3275, 2956, 1620, 1563, 1458 cm^{-1}. HRMS (EI): calcd for $C_{16}H_{18}N_2O$ $[M]^+$ 254.1419, found 254.1419.

*2-(2-(4-(3-Methylbut-2-en-1-yl)-2-oxoindolin-3-yl)ethyl)-isoindoline-1,3-dione (**17b**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (500 mg, 1.34 mmol) **16b** gave product **17b** in 74% yield (370 mg, 0.99 mmol) based on recovered starting material. Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (30 mg, 0.08 mmol) **16b** gave product **17b** in 75% yield (22.5 mg, 0.06 mmol) as a yellow solid (mp 184 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (br s, 1H), 7.76−7.70 (m, 2H), 7.64−7.56 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.7 (d, J = 8.1 Hz, 1H), 6.7 (d, J = 8.0 Hz, 1H), 5.21 (t, J = 7.0 Hz, 1H), 3.71 (ABX, J = 13.5, 6.7 Hz, 1H), 3.66 (ABX, J = 13.5, 7.0 Hz, 1H), 3.61 (t, J = 5.0 Hz, 1H), 3.41 (ABX, J = 16.0, 7.4 Hz, 1H), 3.29 (ABX, J = 16.0, 6.8 Hz, 1H), 2.55 (AB, J = 6.8 Hz, 1H), 2.51 (AB, J = 6.8 Hz, 1H), 1.72 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 168.1 (2 × C), 142.0, 138.5, 133.8 (2 × C), 133.7, 132.1 (2 × C), 128.2, 125.7, 123.1 (3 × C), 121.5, 108.1, 44.0, 34.7, 31.4, 27.2, 25.8, 18.1. FT-IR (KBr, ν_{max}): 3275, 2923, 1713, 1620, 1462, 1370, 752 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$ 374.1630, found 374.1633.

*N,4-Dimethyl-N-(2-(4-(3-methylbut-2-en-1-yl)-2-oxoindolin-3-yl)-ethyl)benzenesulfonamide (**17c**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (100 mg, 0.24 mmol) **16c** gave product **17c** in 57% yield (57 mg, 0.14 mmol) based on recovered starting material. Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (7.0 mg, 0.017 mmol) **16c** gave product **17c** in 40% yield (2.8 mg, 0.007 mmol) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br s, 1H), 7.63−7.49 (m, 2H), 7.28 7.23 (m, 2H), 7.17 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.29−5.21 (m, 1H), 3.59 (dd, J = 7.7, 3.2 Hz, 1H), 3.44 3.28 (m, 2H), 3.08−2.90 (m, 2H), 2.70 (s, 3H), 2.50−2.40 (m, 1H), 2.38 (s, 3H), 2.21−2.06 (m, 1H), 1.74 (d, J = 1.2 Hz, 3H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 143.4, 141.6, 138.8, 134.4, 133.9, 129.7 (2 × C), 128.5, 127.6 (2 × C), 125.8, 123.4, 121.6, 107.6, 46.9, 43.3, 35.5, 31.4, 27.8, 25.9, 21.6, 18.2. FT-IR (KBr, ν_{max}): 3275, 2923, 1713, 1620, 1462, 1370, 1148, 752 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{28}N_2O_3S$ $[M]^+$ 412.1821, found 412.1826.

*Ethyl 3-(4-(3-Methylbut-2-en-1-yl)-2-oxoindolin-3-yl)propanoate (**17d**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (7.0 mg, 0.023 mmol) **16d** gave product **17d** in 52% yield (3.6 mg, 0.012 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (6.0 mg, 0.02 mmol) **16d** gave product **17d** in 42% yield (2.5 mg, 0.008 mmol) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.17−7.11 (m, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 5.22 (tdd, J = 5.7, 2.8, 1.4 Hz, 1H), 4.12−3.94 (m, 2H), 3.61 (dd, J = 6.8, 3.4 Hz, 1H), 3.36 (ddd, J = 23.6, 16.1, 7.1 Hz, 2H), 2.52−2.42 (m, 1H), 2.40−2.24 (m, 2H), 2.23−2.14 (m, 1H), 1.73 (d, J = 1.6 Hz, 6H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8, 173.0, 141.7, 138.9, 133.6, 128.5, 126.1, 123.8, 121.7, 107.6, 60.6, 44.7, 31.4, 29.6, 25.8, 24.6, 18.1, 14.3. FT-IR (KBr, ν_{max}): 3275, 2956, 2855, 1713, 1620, 1563, 1458, 1370 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_3$ $[M]^+$ 301.1678, found 301.1677.

*4-(3-Methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**17e**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (92 mg, 0.34 mmol) **16e** gave product **17e** in 43% yield (39.6 mg, 0.15 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (10 mg, 0.04 mmol) **16e** gave product **17e** in 46% yield (4.6 mg, 0.016 mmol) as a colorless solid (mp 123 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 5.24−5.16 (m, 1H), 3.56 (dd, J = 7.6, 3.5 Hz, 1H), 3.35 (ddd, J = 24.0, 16.8 Hz, 2H), 2.61−2.48 (m, 1H), 2.46−2.26 (m, 2H), 2.23−2.12 (m, 1H), 2.06 (s, 3H), 1.73 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 180.1, 141.6, 139.1, 133.6, 128.4, 126.5, 123.4, 121.7, 107.6, 44.5, 38.6, 31.3, 30.2, 25.9, 23.5, 18.1. FT-IR (KBr, ν_{max}): 3275, 2956, 1713, 1620, 1563, 1458, 1148 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1572, found 271.1571.

*3-Methyl-4-(3-methylbut-2-en-1-yl)indolin-2-one (**17f**).* C3-reverse-prenyl methyloxindole **16f** was prepared according to published methods.[8] Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (56 mg, 0.26 mmol) **16f** gave product **17f** in 32% yield (16.6 mg, 0.08 mmol).[12] Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (7.0 mg, 0.023 mmol) **16f** gave product **17f** in 16% yield (1.1 mg, 0.005 mmol)[12] as a colorless solid (mp 124 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (br s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.27 5.21 (m, 1H), 3.47 (q, J = 7.6 Hz, 1H), 3.40 (ABX, J = 16.0, 7.4 Hz, 1H), 3.30 (ABX, J = 16.0, 6.6 Hz, 1H), 1.74 (d, J = 1.2 Hz, 3H), 1.73 (br s, 3H), 1.53 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 141.2, 138.6, 133.4, 129.0, 128.1, 123.2, 121.9, 107.6, 40.8, 31.3, 25.8, 18.1, 15.5. FT-IR (KBr, ν_{max}): 3162, 3028, 2984, 2915, 1717, 1684, 1620, 1455 cm^{-1}. HRMS (EI): calcd for $C_{14}H_{17}NO$ $[M]^+$ 215.1310, found 215.1314.

*Methyl 4-(3-Methylbut-2-en-1-yl)-2-oxo-3-(3-oxobutyl)indoline-6-carboxylate (**17g**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (94.0 mg, 0.29 mmol) **16g** gave product **17g** in 43% yield (40.4 mg, 0.12 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (31 mg, 0.09 mmol) **16g** gave product **17g** in 40% yield (12.4 mg, 0.04 mmol) as a pale yellow solid (mp 90 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.58 (d, J = 0.8 Hz, 1H), 7.39 (d, J = 1.4 Hz, 1H), 5.23−5.16 (m, 1H), 3.91 (s, 3H), 3.60 (dd, J = 8.0, 3.7 Hz, 1H), 3.44 (ddd, J = 18.5, 15.8, 6.9 Hz, 1H), 2.60 (ddd, J = 14.0, 9.8, 6.0 Hz, 1H), 2.50−2.38 (m, 1H), 2.38 2.28 (m, 1H), 2.20−2.08 (m, 1H), 2.08 (s, 3H), 1.74 (d, J = 0.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 179.4, 166.9, 141.8, 139.2, 134.3, 131.8, 130.5, 125.2, 121.1, 108.1, 52.4, 44.4, 38.5, 31.3, 30.2, 25.9, 23.4, 18.2; HRMS (EI): calcd for $C_{19}H_{23}NO_4$ $[M]^+$ 329.1627, found 329.1622.

*6-Fluoro-4-(3-methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**17h**).* Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (22 mg, 0.076 mmol) **16h** gave product **17h** in 40% yield (8.8 mg, 0.03 mmol) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 6.56 (dd, J = 10.7, 2.3 Hz, 1H), 6.46 (dd, J = 8.3, 2.3 Hz, 1H), 5.26−5.12 (m, 1H), 3.54 3.48 (m, 1H), 3.40−3.25 (m, 2H), 2.63−2.52 (m, 1H), 2.45−2.28 (m, 2H), 2.17−2.09 (m, 1H), 2.08 (s, 3H), 1.74 (d, J = 1.1 Hz, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 179.8, 164.3, 161.8, 142.3, 140.9, 134.5, 121.8, 120.9, 109.4, 96.2, 43.8, 38.5, 31.2, 25.9, 23.7, 18.1. FT-IR (KBr, ν_{max}): 3262, 2923, 2253, 1715, 1614, 1450, 1123 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{20}FNO_2$ $[M]^+$ 289.1478, found 289.1478.

*6-Chloro-4-(3-methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**17i**).* Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (83 mg, 0.27 mmol) **16i** gave product **17i** in 45% yield (37.4 mg, 0.12 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 6.84 (d, J = 1.8 Hz, 1H), 6.72 (d, J = 1.8 Hz, 1H), 5.17 (ddd, J = 7.1, 4.2, 1.5 Hz, 1H), 3.52 (dd, J = 7.9, 3.5 Hz, 1H), 3.4 3.24 (m, 2H), 2.64−2.53 (m, 1H), 2.46−2.28 (m, 2H), 2.16−2.06 (m, 4H), 1.74 (d, J = 1.3 Hz, 3H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 179.3, 142.3, 140.6, 134.5, 133.9, 124.9, 123.2, 120.8, 108.0, 43.9, 38.5, 31.1, 30.2, 25.9, 23.6, 18.2. HRMS (EI): calcd for $C_{17}H_{20}ClNO_2$ $[M]^+$ 305.1183, found 305.1182.

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

*7-Methyl-4-(3-methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**17j**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (100 mg, 0.35 mmol) **16j** gave product **17j** in 60% yield (60 mg, 0.21 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (8.0 mg, 0.028 mmol) **16j** gave product **17j** in 50% yield (4.0 mg, 0.014 mmol) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 5.24−5.14 (m, 1H), 3.57 (dd, J = 7.8, 3.4 Hz, 1H), 3.31 (ddd, J = 22.0, 15.9, 5.6 Hz, 2H), 2.60−2.50 (m, 1H), 2.37 (dddd, J = 30.0, 17.1, 9.5, 4.0 Hz, 2H), 2.22 (s, 3H), 2.20−2.10 (m, 1H), 2.06 (s, 3H), 1.72 (d, J = 1.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 180.4, 140.3, 136.2, 133.4, 129.8, 126.1, 123.3, 122.0, 116.6, 44.8, 38.6, 31.1, 30.2, 25.9, 23.5, 18.1, 16.4. FT-IR (KBr, ν_{max}): 3162, 3049, 2972, 2915, 2851, 1692, 1630, 1595, 1426 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_2$ $[M]^+$ 285.1729, found 285.1727.

*5-Methoxy-4-(3-methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**17k**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (62 mg, 0.21 mmol) **16k** gave product **17k** in 45% yield (28 mg, 0.09 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (15 mg, 0.05 mmol) **16k** gave product **17k** in 48% yield (7.2 mg, 0.023 mmol) as a pale yellow solid (mp 140 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.10 5.02 (m, 1H), 3.79 (s, 3H), 3.57 (dd, J = 7.3, 3.5 Hz, 1H), 3.38 3.29 (m, 2H), 2.55−2.34 (m, 2H), 2.32−2.22 (m, 1H), 2.21−2.10 (m, 1H), 2.05 (s, 3H), 1.75 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 179.6, 153.9, 134.8, 132.7, 128.7, 128.6, 121.7, 109.9, 107.2, 56.2, 44.9, 38.6, 30.1, 26.0, 25.9, 23.8, 18.1. FT-IR (KBr, ν_{max}): 3275, 2933, 1737, 1620, 1563, 1491, 1370, 1244 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{23}NO_3$ $[M]^+$ 301.1678, found 301.1674.

*(Z)-2-(2-(4-(3,7-Dimethylocta-2,6-dien-1-yl)-2-oxoindolin-3-yl)-ethyl)isoindoline-1,3-dione (**17p**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (60 mg, 0.27 mmol) **16p** gave product **17p** in 55% yield (33 mg, 0.075 mmol) as a mixture of E and Z isomers (E:Z = 17:83). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (50 mg, 0.113 mmol) **16p** gave product **17p** in 50% yield (25 mg, 0.056 mmol) as a mixture of E and Z isomers (E:Z = 23:77) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 7.78−7.70 (m, 2H), 7.67−7.59 (m, 2H), 7.01 (t, J = 7.8 Hz, 1H), 6.74−6.63 (m, 2H), 5.26 5.20 (m, 1H), 5.16−5.02 (m, 1H), 3.76−3.58 (m, 3H), 3.47−3.26 (m, 2H), 2.61−2.45 (m, 2H), 2.20−1.98 (m, 4H), 1.72 (m, 3H), 1.67 (s, 3H), 1.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 168.1 (2 × C), 141.8, 138.7, 137.6, 133.8 (2 × C), 132.1 (2 × C), 131.9, 128.3, 125.7, 124.2, 123.3, 123.2 (2 × C), 121.9, 107.9, 43.9, 34.7, 32.1, 30.9, 27.3, 26.6, 25.9, 23.5, 17.8. FT-IR (KBr, ν_{max}): 2919, 1769, 1716, 1616, 1450, 1398, 718 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{30}N_2O_3$ $[M]^+$ 442.2256, found 442.2258.

*(Z)-2-(2-(4-(3,7-Dimethylocta-2,6-dien-1-yl)-2-oxoindolin-3-yl)-ethyl)isoindoline-1,3-dione (**17q**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (140 mg, 0.32 mmol) **16q** gave product **17q** in 46% yield (64.4 mg, 0.145 mmol) as a mixture of E and Z isomers (E:Z = 83:17). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (24 mg, 0.054 mmol) **16q** gave product **17q** in 62% yield (14.9 mg. 0.034 mmol) as a mixture of E and Z isomers (E:Z = 77:23) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (br s, 1H), 7.76−7.70 (m, 2H), 7.64−7.57 (m, 2H), 7.01 (t, J = 7.8 Hz, 1H), 6.76−6.60 (m, 2H), 5.27−5.18 (m, 1H), 5.16−5.00 (m, 1H), 3.77−3.57 (m, 3H), 3.48−3.26 (m, 2H), 2.58−2.46 (m, 2H), 2.17−1.99 (m, 4H), 1.74−1.69 (m, 3H), 1.66 (d, J = 1.0 Hz, 3H), 1.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 168.0 (2 × C), 141.9, 138.5, 137.4, 133.8 (2 × C), 132.1 (2 × C), 131.7, 128.2, 125.7, 124.2, 123.1 (2 × C), 121.4, 108.1, 44.0, 39.7, 34.7, 31.3, 27.1, 26.6, 25.8, 17.8, 16.4. FT-IR (KBr, ν_{max}): 3246, 2968, 2923, 2851, 2366, 2334, 1773, 1733, 1705, 1616, 1596, 1453, 1400, 1113, 1018, 721 cm^{-1}. HRMS (EI): calcd for $C_{28}H_{30}N_2O_3$ $[M]^+$ 442.2256, found 442.2251.

*2-(2-(2-Oxo-4-((2Z,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-indolin-3-yl)ethyl)isoindoline-1,3-dione (**17r**).* Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (75 mg, 0.147 mmol) **16r** gave product **17r** in 52% yield (39 mg, 0.076 mmol) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77−7.70 (m, 3H), 7.65 7.62 (m, 2H), 7.00 (t, J = 7.8 Hz, 1H), 6.72−6.61 (m, 2H), 5.26 5.04 (m, 3H), 3.78−3.58 (m, 3H), 3.47−3.26 (m, 2H), 2.63−2.45 (m, 2H), 2.21−1.91 (m, 8H), 1.75−1.70 (m, 3H), 1.67 (s, 3H), 1.61−1.56 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 168.0 (2 × C), 141.8, 138.7, 137.7, 135.6, 133.8 (2 × C), 132.1 (2 × C), 131.5, 128.3, 125.7, 124.5, 124.0, 123.3, 123.2 (2 × C), 121.9, 107.9, 43.9, 39.9, 34.7, 32.2, 31.0, 27.3, 26.9, 26.5, 25.9, 23.6, 17.9, 16.2. FT-IR (KBr, ν_{max}): 3258, 2921, 2851, 1773, 1716, 1620, 1596, 1452, 1399, 1107, 718.8 cm^{-1}. HRMS (EI): calcd for $C_{33}H_{38}N_2O_3$ $[M]^+$ 510.2882, found 510.2885.

*Methyl 2-(1,3-Dioxoisoindolin-2-yl)-3-(4-(3-methylbut-2-en-1-yl)-2-oxoindolin-3-yl)propanoate (**17s**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (1.0 g, 2.31 mmol) **16s** gave product **17s** in 61% yield (610 mg, 1.41 mmol). Following general procedure C, under microwave conditions, C3-reverse prenyl oxindole (50.0 mg, 0.12 mmol) **16s** gave product **17s** in 54% yield (27.0 mg, 0.06 mmol) as a 1:1 mixture of diastereomers as a colorless solid (mp 220 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.68 (br s, 1H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.67−7.58 (m, 4H), 7.47 (dd, J = 5.5, 3.0 Hz, 2H), 7.20 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.7 Hz, 1H), 6.61 (t, J = 7.8 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 6.38 (d, J = 7.9 Hz, 1H), 5.24 (t, J = 6.9 Hz, 1H), 5.12 (t, J = 6.9 Hz, 1H), 5.05 (dd, J = 9.4, 5.6 Hz, 1H), 4.79 (dd, J = 11.8, 2.5 Hz, 1H), 3.75−3.70 (m, 1H), 3.71 (s, 3H), 3.69−3.65 (m, 1H), 3.68 (s, 3H), 3.58 (dd, J = 7.6, 2.8 Hz, 1H), 3.43 (ABX, J = 15.7, 6.8 Hz, 1H), 3.39−3.27 (m, 4H), 3.22 (ABX, J = 16.0, 6.8 Hz, 2H), 1.74 (s, 6H), 1.73 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 178.7, 169.5, 169.3 (2 × C), 167.2, 167.1 (2 × C), 142.1, 141.5, 138.8, 138.3, 134.0, 133.9 (2 × C), 133.8 (2 × C), 131.9 (2 × C), 131.7 (2 × C), 128.9, 127. 7 (2 × C), 125.7, 124.8, 123.5 (2 × C), 123.2, 123.2 (2 × C), 123.1, 121.4 (2 × C), 108.4, 108.0, 53.1, 53.0, 48.9, 48.7, 43.4, 43.3, 31.5, 31.2, 27.8, 27.5, 25.9, 25.8, 18.1, 18.1. FT-IR (KBr, ν_{max}): 3428, 2923, 1713, 1620, 1563, 1462, 1370, 752 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{24}N_2O_5$ $[M]^+$ 432.1685, found 432.1684. HPLC: t_R for each diastereomer 8.8 min (major) and 12.9 min (minor) (Chiralpak AS column, 30% ^{i}PrOH/Hex). A detailed assignment of proton NMR signals is provided in Table S2 (Supporting Information).

*N-Methyl-N-(2-(4-(3-Methylbut-2-en-1-yl)-2-oxoindolin-3-yl)-ethyl)-4-nitrobenzenesulfonamide (**17t**).* Following general procedure B, under thermal rearrangement conditions, C3-reverse prenyl oxindole (100 mg, 0.225 mmol) **16t** gave product **17t** in 50% yield (50 mg, 0.112 mmol)[12] as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38−8.28 (m, 2H), 7.94 (s, 1H), 7.90−7.84 (m, 2H), 7.18 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 5.29−5.21 (m, 1H), 3.60 (dd, J = 7.7, 3.2 Hz, 1H), 3.44 3.28 (m, 2H), 3.16−2.97 (m, 2H), 2.78 (s, 3H), 2.53−2.38 (m, 1H), 2.23−2.11 (m, 1H), 1.76 (d, J = 1.1 Hz, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.02, 150.1, 143.5, 141.5, 138.9, 134.0, 128.7, 128.6 (2 × C), 125.5, 124.5 (2 × C), 123.6, 121.4, 107.8, 46.9, 43.2, 35.4, 31.4, 27.7, 25.9, 18.2. FT-IR (KBr, ν_{max}): 3444, 2923, 1707, 1596, 1531, 1455, 1350, 1163, 738 cm^{-1}. HRMS (EI): calcd for $C_{22}H_{25}N_3O_5S$ $[M]^+$ 443.1515, found 443.1511.

*C3-n-Prenylated Products of [1,3]-Prenyl Transfer Reaction. 2-(2-(3-(3-Methylbut-2-en-1-yl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (**18b**).* Following general procedure D, under thermal rearrangement conditions in decalin, C3-reverse prenyl oxindole (50 mg, 0.13 mmol) **16b** gave product **18b** in 65% yield (32.5 mg, 0.087 mmol) as a colorless solid (mp 167 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.66 (m, 2H), 7.65−7.59 (m, 2H), 7.54 (s, 1H), 7.11−7.05 (m, 1H), 6.98−6.91 (m, 1H), 6.79−6.71 (m, 2H), 4.88−4.80 (m, 1H), 3.68−3.43 (m, 2H), 2.53−2.41 (m, 3H), 2.33−2.24 (m, 1H), 1.56 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 168.0 (2 × C), 140.7, 136.0, 133.8 (2 × C), 132.1 (2 × C), 131.6, 127.7, 123.4, 123.1 (2 × C), 122.3, 117.1, 109.8, 52.0, 37.4, 34.5, 33.6, 26.0, 18.1. HRMS (EI): calcd for $C_{23}H_{22}N_2O_3$ $[M]^+$ 374.1630, found 374.1633.

dx.doi.org/10.1021/jo501651z | J. Org. Chem. 2014, 79, 10049−10067

*3-Methyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (**18f**).* Following general procedure D, under thermal rearrangement conditions in decalin, C3-reverse prenyl oxindole (56 mg, 0.26 mmol) **16f** gave product **18f** in 98% yield (55 mg, 0.25 mmol) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.22−7.14 (m, 2H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.91−6.84 (m, 1H), 4.92−4.82 (m, 1H), 2.49 (qd, J = 14.2, 7.5 Hz, 2H), 1.58 (d, J = 1.0 Hz, 3H), 1.52 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 140.2, 135.4, 134.7, 127.7, 123.5, 122.4, 118.2, 109.5, 49.0, 36.8, 26.0, 22.8, 18.1. FT-IR (KBr, ν_{max}): 3210, 2916, 2850, 1710, 1620, 1463, 1377 cm^{-1}. HRMS (EI): calcd for $C_{14}H_{17}NO$ $[M]^+$ 215.1310, found 215.1308.

*6-Fluoro-3-(3-methylbut-2-en-1-yl)-3-(3-oxobutyl)indolin-2-one (**18h**).* In an attempt to obtain the [3,3]-rearrangement product **17h** following general procedure B, under thermal rearrangement conditions in DMAc, C3-reverse prenyl oxindole (22 mg, 0.076 mmol) **16h** gave product **18h** (as a minor product) in 20% yield as a colorless oil. This product was verified as the [1,3]-rearrangement product through spectral analysis as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.06 (dd, J = 8.2, 5.3 Hz, 1H), 6.78−6.69 (m, 1H), 6.63 (dd, J = 8.7, 2.3 Hz, 1H), 4.86 4.78 (m, 1H), 2.50 (ddd, J = 20.9, 14.1, 7.6 Hz, 2H), 2.34−2.23 (m, 1H), 2.15 (dd, J = 8.9, 6.7 Hz, 2H), 2.03−1.91 (m, 4H), 1.58 (s, 3H), 1.50 (s, 3H). HRMS (EI): calcd for $C_{17}H_{20}FNO_2$ $[M]^+$ 289.1478, found 289.1473.

*(E)-2-(2-(3-Cinnamyl-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione (**18l**).* Following general procedure B, under thermal rearrangement conditions in DMAc, C3-reverse prenyl oxindole (45 mg, 0.107 mmol) **16l** gave product **18l** in 46% yield (20.7 mg, 0.05 mmol) as a colorless oil as the *only* product, and no [3,3]-rearrangement was observed. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.71−7.65 (m, 2H), 7.64−7.60 (m, 2H), 7.24−7.11 (m, 6H), 6.97 (td, J = 7.7, 1.2 Hz, 1H), 6.83−6.74 (m, 2H), 6.33 (d, J = 15.8 Hz, 1H), 5.86 (dt, J = 15.5, 7.6 Hz, 1H), 3.57 (tdd, J = 14.0, 10.7, 6.2 Hz, 2H), 2.71−2.60 (m, 2H), 2.54−2.44 (m, 1H), 2.40−2.31(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 168.0 (2 × C), 140.7, 137.2, 134.4, 133.8 (2 × C), 132.0 (2 × C), 131.1, 128.5 (2 × C), 128.0, 127.4, 126.4 (2 × C), 123.4, 123.1 (2 × C), 122.5, 110.1, 52.2, 42.3, 34.4, 33.7; FTIR (KBr, ν_{max}): 3432, 2253, 1713, 1620, 1470, 911.7 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{22}N_2O_3$ $[M]^+$ 422.1630, found 422.1627.

*C3-n-Prenylated Products of [1,3]-Prenyl Transfer Reaction on C3-Hydroxy Substrates. 5-Bromo-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one (**21b**).* Prenyl bromide (400 μL, 3.55 mmol) was added to a magnetically stirred solution of 5-bromoisatin (400 mg, 1.78 mmol), indium powder (255 mg, 2.22 mmol), and sodium iodide (531 mg, 3.55 mmol) in DMF (5 mL) at 0 °C. The resulting mixture was stirred at the same temperature until complete disappearance of starting material (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added, and the mixture was warmed to room temperature before being extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting mass was subjected to silica gel chromatography (17% ethyl acetate in hexanes) to give the purified product **21b** in 57% isolated yield as a pale oil. ^{1}H NMR (400 MHz, CD_3OD): δ 7.41 (dd, J = 2.0, 0.4 Hz, 1H), 7.37 (dd, J = 8.2, 2.0 Hz, 1H), 6.75 (dd, J = 8.2, 0.4 Hz, 1H), 6.09 (dd, J = 17.6, 10.9 Hz, 1H), 5.06 (dd, J = 10.9, 1.4 Hz, 1H), 4.95 (dd, J = 17.6, 1.4 Hz, 1H), 1.22 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 181.3, 143.5, 142.5, 134.4, 133.0, 130.1, 114.9, 114.2, 112.2, 81.4, 44.2, 21.9, 20.6. FT-IR (KBr, ν_{max}): 3347, 3230, 2988, 1702, 1616, 1475, 1442, 1313, 1170 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{14}BrNO_2$ $[M]^+$ 295.0208, found 295.0214.

*5-Chloro-3-hydroxy-3-(2-methylbut-3-en-2-yl)indolin-2-one (**21c**).* Colorless solid (mp 230 °C), 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H), 7.20 (dd, J = 8.2, 2.2 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 5.98 (s, 1H, −OH), 5.98 (dd, J = 17.6, 11.2 Hz, 1H), 4.99 (dd, J = 10.8, 1.4 Hz, 1H), 4.86 (dd, J = 17.6, 1.5 Hz, 1H), 1.14 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.4, 142.5, 141.1, 133.1, 128.5, 125.6, 124.6, 113.1, 110.4, 79.1, 42.7, 21.2, 19.8. FT-IR (KBr, ν_{max}): 3347, 3230, 2988, 1702, 1616, 1475, 1442, 1313, 1170 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{14}ClNO_2$ $[M]^+$ 251.0713, found 251.0714.

*3-Hydroxy-3-(3-methylbut-2-en-1-yl)indolin-2-one (**22a**).* Precursor **21a** was synthesized according to published methods.[6] Following general procedure D, under thermal rearrangement conditions in decalin, C3-reverse prenyl oxindole (78 mg, 0.36 mmol) **21a** gave product **22a** in 50% yield (39 mg, 0.18 mmol) as a colorless oil. Microwave irradiation (at the same power levels as in procedure C) of C3-reverse prenyl oxindole (6.0 mg, 0.03 mmol) **21a** in phosphate buffer provided product **22a** in 89% yield (5.3 mg, 0.025 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.39−7.34 (m, 1H), 7.28−7.23 (m, 1H), 7.07 (td, J = 7.5, 0.9 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 5.05−5.01 (m, 1H), 2.85 (s, 1H, exchangeable with D_2O), 2.65 (d, J = 7.6 Hz, 2H), 1.67 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.8, 140.3, 137.7, 130.6, 129.7, 124.6, 123.1, 115.7, 110.1, 76.5, 37.5, 26.1, 18.1. FT-IR (KBr, ν_{max}): 3238, 2919, 1705, 1616, 1475, 1115 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103, found 217.1106.

*5-Bromo-3-hydroxy-3-(3-methylbut-2-en-1-yl)indolin-2-one (**22b**).* Precursor **21b** was synthesized according to published methods.[6] Following general procedure B/D, under thermal rearrangement conditions in DMAc or decalin, C3-reverse prenyl oxindole (28 mg, 0.095 mmol) **21b** gave product **22b** in 50% yield (14 mg, 0.047 mmol) as a colorless oil. Microwave irradiation (at the same power levels as in procedure C) of C3-reverse prenyl oxindole (15.0 mg, 0.05 mmol) **21b** in phosphate buffer provided product **22b** in 75% yield (11.3 mg, 0.038 mmol). ^{1}H NMR (400 MHz, CD_3OD): δ 7.44−7.42 (m, 1H), 7.38 (dd, J = 8.2, 2.1 Hz, 1H), 6.80 6.76 (m, 1H), 4.87−4.80 (m, 1H), 2.61 (d, J = 7.6 Hz, 2H), 1.59 (d, J = 1.0 Hz, 3H), 1.49 (d, J = 0.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.6, 140.9, 134.8, 134.3, 131.4, 126.9, 116.8, 113.2, 111.4, 75.7, 36.3, 25.7, 17.8. HRMS (EI): calcd for $C_{13}H_{14}BrNO_2$ $[M]^+$ 295.0208, found 295.0207.

*5-Chloro-3-hydroxy-3-(3-methylbut-2-en-1-yl)indolin-2-one (**22c**).* Precursor **21c** was synthesized according to published methods.[6] Following general procedure B/D, under thermal rearrangement conditions in DMAc or decalin, C3-reverse prenyl oxindole (33 mg, 0.13 mmol) **21c** gave product **22c** in 41% yield (13.5 mg, 0.053 mmol) as colorless oil as the *only* product, and no [3,3]-rearrangement was observed. Microwave irradiation (at the same power levels as in procedure C) of C3-reverse prenyl oxindole (9.0 mg, 0.035 mmol) **21c** in phosphate buffer provided product **22a** in 87% yield (7.8 mg, 0.03 mmol). ^{1}H NMR (400 MHz, CD_3OD): δ 7.30 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.3, 2.2 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.88−4.77 (m, 1H), 2.61 (d, J = 7.6 Hz, 2H), 1.58 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 181.7, 141.5, 137.7, 134.8, 130.1, 128.7, 125.6, 117.2, 112.1, 77.9, 37.6, 26.0, 18.0. FT-IR (KBr, ν_{max}): 3358, 2493, 2245, 2209, 2072, 1123, 976 cm^{-1}. HRMS (EI): calcd for $C_{13}H_{14}ClNO_2$ $[M]^+$ 251.0713, found 251.0705.

*C3-n-Prenyl-L-Trp-pyrroloindoline Methyl Ester (**13** and **14**).* Following general procedure E, treatment of L-trp-methyl ester (400 mg, 1.83 mmol) **11** gave products **13** and **14** (in a 4:1 ratio) as mixture of diastereomers in 67% overall yield (358 mg, 1.25 mmol) (based on recovered starting material) as a pale oil. Data for major diastereomer **13** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06−7.01 (m, 2H), 6.72 (dt, J = 7.4, 0.9 Hz, 1H), 6.56 (d, J = 7.9 Hz, 1H), 5.09 (t, J = 7.3 Hz, 1H), 4.91 (s, 1H), 3.71 (dd, J = 10.5, 5.8 Hz, 1H), 3.70 (s, 3H), 3.42 (br s, 2H), 2.47−2.41 (m, 2H), 2.38 (dd, J = 12.0, 5.8 Hz, 1H), 2.00 (dd, J = 12.0, 10.7 Hz, 1H), 1.68 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 150.0, 134.7, 133.1, 128.2, 123.6, 119.6, 118.8, 109.1, 82.2, 59.4, 58.8, 52.2, 44.2, 36.9, 26.0, 18.2. FT-IR (KBr, ν_{max}): 3366, 3044, 2933, 1823, 1737, 1672, 1605, 1477, 1365, 1225, 1110, 1024, 942, 833, 747 cm^{-1}. HRMS (ESI+): calcd for $C_{17}H_{23}O_2N_2$ $[M + H]^+$ 287.1681, found 287.1683.

*N1-Me-C3-n-Prenyl-L-Trp-pyrroloindoline Methyl Ester (**28** and **29**).* Following general procedure E, treatment of *N*-Me L-Trp-methyl ester **27** (680 mg, 2.93 mmol) gave product **28** in 21% yield and **29** in 11% yield as a diastereomeric mixture as a pale oil along with a 40% recovery of **27** amounting to a 53% overall yield (466 mg, 1.55 mmol). Data for diastereoisomer **28** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dt, J = 7.7, 1.2 Hz, 1H), 7.00 (dd, J = 7.3, 1.2 Hz, 1H), 6.63 (dt, J = 7.4, 0.9 Hz, 1H), 6.34 (d, J = 7.8 Hz, 1H), 5.09 (qt, J = 6.7, 1.3 Hz, 1H), 4.67 (s, 1H), 3.71 (s, 3H), 3.66 (dd, J = 10.3, 6.2

Hz, 1H), 3.08 (br s, 1H), 2.83 (s, 3H), 2.45−2.38 (m, 2H), 2.35 (dd, J = 12.2, 6.2 Hz, 1H), 2.00 (t, J = 11.2 Hz, 1H), 1.68 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 151.20, 134.6, 133.4, 128.3, 123.0, 119.7, 117.0, 105.6, 88.8, 59.5, 57.1, 52.2, 44.0, 36.7, 31.7, 26.0, 18.2. FT-IR (KBr, ν_{max}): 3366, 3044, 2933, 1823, 1737, 1672, 1605, 1477, 1365, 1225, 1110, 1024, 942, 833, 747, 662 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{24}O_2N_2$ $[M]^+$ 300.1838, found 300.1838. Data for diastereoisomer **29** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (dt, J = 7.6, 1.2 Hz, 1H), 6.98 (dd, J = 7.3, 0.9 Hz, 1H), 6.60 (dt, J = 7.4, 0.8 Hz, 1H), 6.29 (d, J = 7.8 Hz, 1H), 5.13 (qt, J = 6.7, 1.2 Hz, 1H), 4.63 (s, 1H), 3.91 (dd, J = 7.8, 3.1 Hz, 1H), 3.50 (br s, 1H), 3.33 (s, 3H), 2.86 (s, 3H), 2.49−2.36 (m, 3H), 2.33 (ABX, J = 12.8, 7.9 Hz, 1H), 1.69 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 150.8, 134.5, 133.6, 128.3, 123.2, 119.9, 117.0, 105.6, 88.7, 60.0, 56.0, 52.0, 41.0, 36.2, 31.4, 26.1, 18.2. FT-IR (KBr, ν_{max}): 3366, 3044, 2933, 1823, 1737, 1672, 1605, 1477, 1365, 1225, 1110, 1024, 942, 833, 747, 662 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{24}O_2N_2$ $[M]^+$: 300.1838, found 300.1838.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving general methods and procedures for all known precursors along with their syntheses, NMR spectra (^{1}H and ^{13}C) of all new compounds, and conversion of compounds **16** and **17** as a function of substituent effects. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ ACKNOWLEDGMENTS

The authors thank Dr. James Faulk (Dept. of Chemistry, Case Western Reserve University) for support with mass spectral data acquisition. D.S. thanks the Department of Chemistry for graduate financial support. We thank Prof. Amy Lane (University of North Florida) and Prof. Eric Schmidt (University of Utah) for informative discussions on mechanistic and biomimetic relevance to prenyltransferases. The authors thank Case Western Reserve University for funding the study.

■ DEDICATION

†Authors dedicate this manuscript to Prof. Jeffrey N. Johnston (VICB) on the occasion of his 2014 Arthur C. Cope Scholar Award.

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