JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

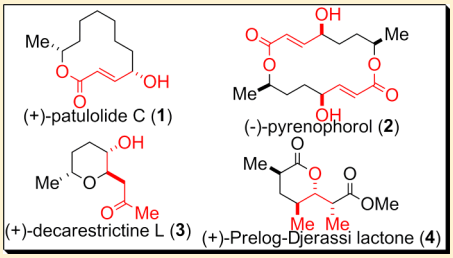
Asymmetric Hydroformylation-Initiated Tandem Sequences for Syntheses of (+)-Patulolide C, (−)-Pyrenophorol, (+)-Decarestrictine L, and (+)-Prelog Djerassi Lactone

Roberto M. Risi,[†] Andrew M. Maza,[†] and Steven D. Burke*,[†]

[†]Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

Supporting Information

ABSTRACT: Four different Rh-catalyzed asymmetric hydroformylation (AHF) tandem reactions have been developed in the context of the total syntheses of (+)-patulolide C, (−)-pyrenophorol, (+)-decarestrictine L, and (+)-Prelog−Djerassi lactone. A total synthesis of (+)-patulolide C has been accomplished in three steps utilizing a Rh(I)-catalyzed *Z*-selective anti-Markovnikov hydroacetoxylation of a known alkyne to give a *Z*-enol acetate with excellent selectivity. An AHF/intramolecular Wittig olefination cascade was utilized to set the C4-hydroxyl stereochemistry, *E*-olefin geometry, and form the macrolactone. In addition, both (−)-pyrenophorol and (+)-decarestrictine L have been synthesized from the enantiomeric (4*R*)- and (4*S*)-4-(*tert*-butyldimethylsiloxy)-1-pentyne in five and four steps, respectively. These syntheses feature Ru(II)-catalyzed *Z*-selective anti-Markovnikov hydroacetoxylation of terminal alkynes followed by AHF/Wittig olefination sequences to rapidly establish functionality and stereogenicity. A synthesis of (+)-Prelog−Djerassi lactone was accomplished in three isolations from the known 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane ortho ester. An AHF/crotylation tandem sequence has been developed to set the C2−C4 stereochemistry. An asymmetric hydrogenation was employed to set the C6 stereochemistry, resulting in an especially efficient enantioselective synthesis from achiral starting material. In summary, these syntheses have greatly improved efficiency in terms of atom-economy, catalytic stereoselective transformations, inexpensive reagents, step-counts, and overall yield when compared with previous synthetic attempts.



INTRODUCTION

A current challenge in synthetic organic chemistry is to synthesize high value target molecules with greater efficiency, higher atom-economy, less waste, lower step-counts, and greater overall yield. Minimization of protection/deprotection steps, oxidation state adjustments, and isolations/purifications helps meet those objectives. Our goal in this work was to demonstrate that asymmetric hydroformylation (AHF) showcasing the Landis Rh(I)−BDP catalyst (Figure 1) can be featured in the synthetic chemist's toolbox to meet that challenge. Herein we describe syntheses of several natural product targets of modest complexity that have been synthesized multiple times, thus affording benchmarks for comparison. The title compounds have served over time to illustrate the utility of a wide variety of synthesis methods and strategies, and a direct comparison of previous efforts with the AHF-based results is described here.

Rhodium(I)-catalyzed hydroformylation[1] is a reaction that converts alkenes into aldehydes via a one-carbon homologation. The reaction yields two possible regioisomers of the aldehyde: the branched isomer (B) and the linear isomer (L) (Scheme 1).

Given their enormous synthetic versatility and the α-chiral center present in the branched aldehydes, these building blocks have high potential for use as intermediates in the synthesis of pharmaceuticals, agrochemicals, ligands, and materials if they are enantioenriched.

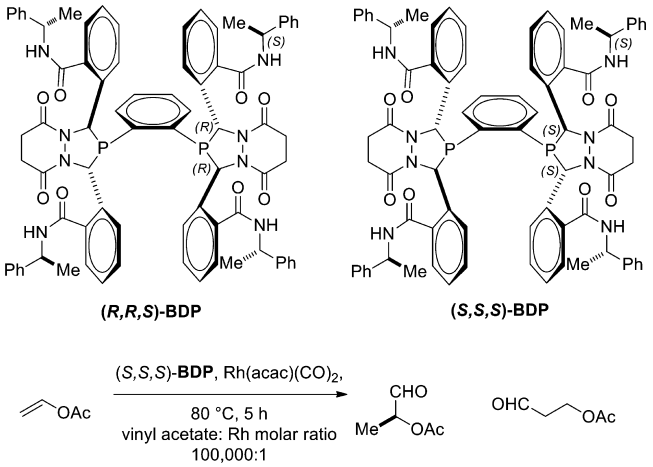


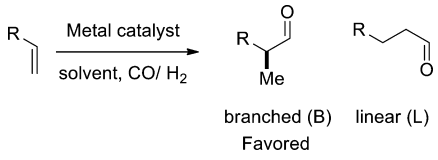
Figure 1. Landis ligands/AHF of vinyl acetate.

Positive attributes of AHF include (1) inexpensive reagents (alkene, H_2 and CO) are used, which makes the reaction economical; (2) it demonstrates excellent atom-economy (i.e., all the atoms in the alkene, H_2, and CO are incorporated into the

Received: October 7, 2014
Published: November 14, 2014

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

Scheme 1. AHF of a Terminal Alkene



aldehyde product); (3) the origin of asymmetric induction is catalytic and not stoichiometric; and (4) reactions with high atom-economy produce less waste, which makes them more environmentally friendly and amenable to large-scale application.[2] The ever-increasing demands for efficient resource utilization and environmental protection necessitate the use of catalytic reactions in synthetic chemistry, especially at the industrial scale,[2] and the efficiency and utility of AHF are noteworthy.

AHF is also highly functional group tolerant. The reaction is usually done under neutral conditions so the newly formed α-chiral aldehyde, as well as any other pH sensitive functionality in the molecule, is relatively safe from isomerization or degradation. Given the versatility of the aldehyde functional group,[3,4] it can serve as an ideal lynchpin for building molecular complexity rapidly. Once the AHF is complete, the excess reagents (CO and H_2) are easily removed by venting the reaction vessel. The aldehyde product is essentially pure, aside from the small amount of catalyst that is generally inert to subsequent transformations, and ready to use without purification. These qualities make the AHF an ideal reaction for developing tandem transformations. In fact, several instances of hydroformylation tandem reactions have been reported including an AHF/asymmetric aldol,[5] hydroformylation/S_N1 alkylation,[6] hydroformylation/asymmetric Mannich,[7] bidirectional hydroformylation/tandem hydrogenation−reductive bis-amination,[8] AHF/crotylation[9,10] and AHF/Wittig olefinations.[11,12] From an industrial perspective, this is highly advantageous because each step requiring purification increases expense, time, and effort, and it generates additional waste. Therefore, eliminating a purification step while building stereochemistry and functionality into the molecule is potentially of great value.

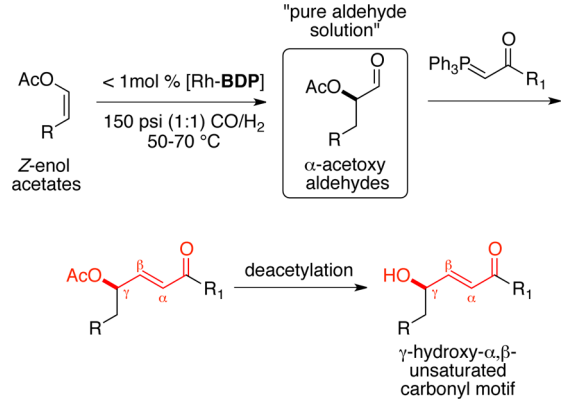
A substantial body of fundamental research has been done in the field of AHF.[13,14] Ideally, in an AHF reaction the catalyst must exert both excellent regio- and enantioselectivity while transforming the alkene substrate. Many of the catalyst systems developed for this purpose still suffer from slow rates, especially on internal alkenes, and low regio- and enantioselectivity for a broad range of substrates.[15] In 2005 and subsequently, Landis described a new, highly active AHF ligand,[16] the bis-3,4-diazaphospholanes shown in Figure 1.

Rhodium-catalyzed AHF with the (*S,S,S*)/(*R,R,S*)-bisdiazaphospholanes (BDP) exhibit exceptional reactivity toward a variety of olefins. Marked by high turnover numbers (TONs), high turnover frequencies (TOFs), and excellent regio- and enantioselectivity, these ligands are among the most successful in the field.

Vinyl acetate has long been a standard hydroformylation substrate, and the Landis group has demonstrated a large-scale Rh(I)-catalyzed AHF with the (*S,S,S*)-BDP ligand on vinyl acetate generating the chiral (2*S*-acetyloxy)propanal with excellent regio- and enantioselectivity (41:1 B:L, 92−96% ee, Figure 1).[16] This catalyst system exhibits outstanding reactivity with substrate to catalyst ratios of up to 150000:1 and TOFs averaging 19400.

The aforementioned characteristics clearly illustrate the selectivity, versatility, and robust nature of the [Rh-BDP] catalyst system for AHF. We saw in this catalyst system an excellent opportunity to dramatically increase synthetic efficiency in natural products total synthesis. Since the [Rh-BDP]-catalyzed AHF worked so well with vinyl acetate (Figure 1) and it was reported that the Wittig olefination of aldehydes in crude AHF mixtures with stabilized phosphorus ylides does not erode enantiopurity via enolization,[11,12] we set out to develop and apply AHF/Wittig olefinations of *Z*-enol acetates to access the γ-hydroxy-α,β-unsaturated carbonyl motifs (Scheme 2), commonly found as structural subunits in natural products such as (+)-patulolide C (**1**), (−)-pyrenophorol (**2**), and (+)-decarestrictine L (**3**) (Figure 2).

Scheme 2. AHF/Wittig Olefination Strategy



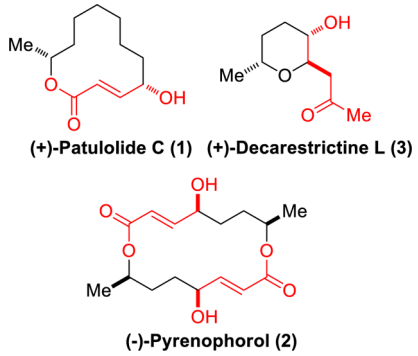


Figure 2. γ-Hydroxy-α,β-unsaturated carbonyl motif in natural products.

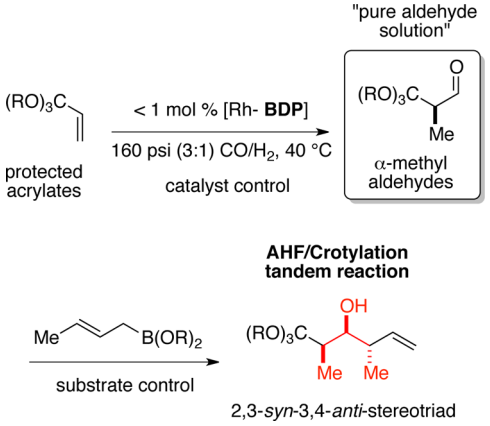
Z-Enol acetates are excellent [Rh-BDP]-catalyzed AHF substrates (vide infra) and can be accessed via the reported *Z*-selective, anti-Markovnikov hydroacetoxylation of terminal alkynes.[17] To specify the details of the envisioned synthesis strategy (Scheme 2), [Rh-BDP]-catalyzed AHF would produce α-acetoxyaldehyde, setting the nascent hydroxyl stereocenter under catalyst control. It was anticipated that once the AHF was complete, venting the reaction vessel followed by addition of the stabilized phosphorus ylide would effect the Wittig olefination installing the α,β-unsaturated carbonyl motif. Simple deacetylation would unveil the γ-hydroxy-α,β-unsaturated carbonyl motif (Scheme 2), which is present in (+)-patulolide C (**1**), (−)-pyrenophorol (**2**), and (+)-decarestrictine L (**3**) as highlighted in red in Figure 2. We set out to develop and apply AHF/Wittig olefinations (both intramolecular and intermolecular) to these three target molecules with a focus on improving

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

step-count and overall yield efficiencies in comparison to previously published approaches.

Also envisioned was the [Rh-BDP]-catalyzed AHF of a masked acrylate (Scheme 3) to generate an α-methyl chiral

Scheme 3. AHF/Crotylation Strategy



aldehyde with a masked 1,3-dicarbonyl unit. Similar α-methyl chiral aldehydes have been used extensively in polypropionate natural product synthesis, and we saw this as an alternative entry into polypropionate arrays via a [Rh-BDP]-catalyzed AHF-initiated tandem reaction.

Some well-known polypropionate natural products are shown in Figure 3 with the characteristic alternating methyl, hydroxyl,

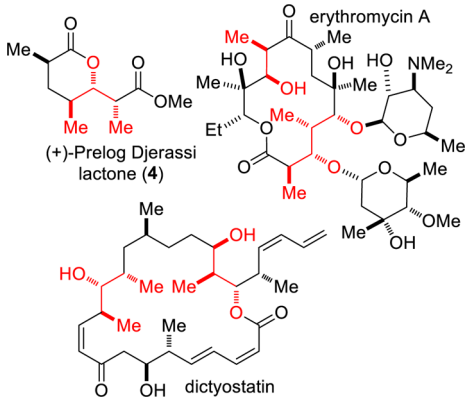


Figure 3. Polypropionate natural products.

and methyl substituent motifs highlighted in red. We sought to develop and apply an AHF/crotylation tandem sequence in the context of a short synthesis of the well-known Prelog–Djerassi lactone (**4**).

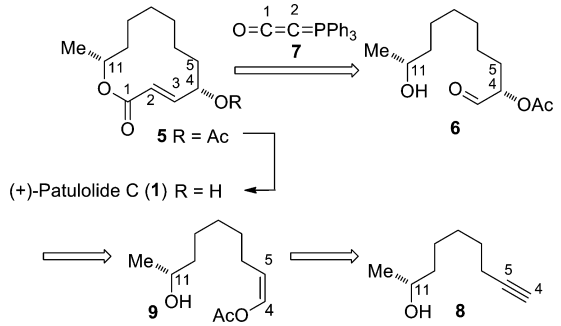
Since the boron-mediated crotylation of α-methyl chiral aldehydes is well-established,[18] we sought to couple these two powerful C–C bond formations in an AHF/crotylation tandem reaction for the rapid synthesis of the methyl-, hydroxyl-, and methyl-bearing stereotriad that is characteristic of polypropionates (Scheme 3). Our plan was to utilize the high enantioselectivity of the BDP ligands to set the first stereocenter in the AHF (catalyst control) followed by a Felkin–Anh selective crotylation[19] (substrate control) to set the other two stereocenters (Scheme 3). We saw the sequential combination of catalyst control and substrate control as an opportunity to telescope the influence of the chiral catalyst from one stereocenter to three stereocenters in a single pot.

Based upon these methodological and strategic considerations, the application of these AHF/tandem reactions to the syntheses of (+)-patulolide C (**1**), (−)-pyrenophorol (**2**), (+)-decarestrictine L (**3**), and the (+)-Prelog–Djerassi lactone (**4**) are presented below.

RESULTS AND DISCUSSION

Synthesis of (+)-Patulolide C. (+)-Patulolide C (**1**, Scheme 4) was first discovered by Yamada and co-workers in 1985 from

Scheme 4. Synthesis Strategy for (+)-Patulolide C (1)



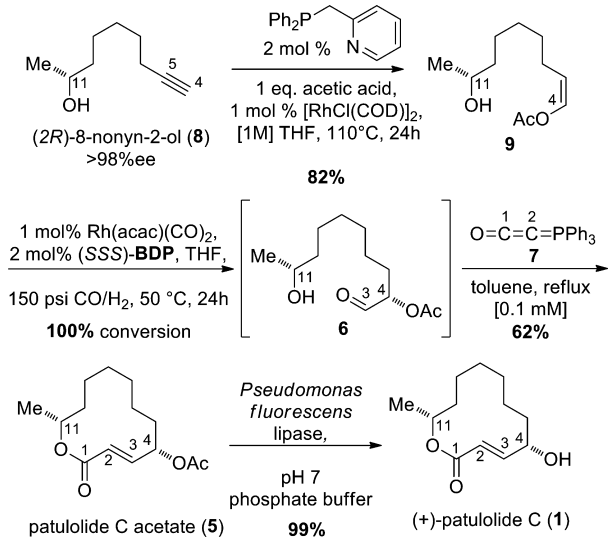
the culture filtrate of *Penicillium urticae* S11R59 mutant, along with its congeners patulolide A and B.[20] (+)-Patulolide C (**1**) is a 12-membered ring lactone containing an *E*-α,β-unsaturated carbonyl, a C11-(*R*) methyl-bearing stereocenter, and a C4 (*S*) secondary carbinol. Exhibiting both antifungal and antibacterial activities,[21] the patulolides have been the targets of several total syntheses. Some strategies for macrocycle formation include utilizing the Yamaguchi macrolactonization,[22,21,23−26] Mitsunobu lactonization,[27] Shiina lactonization,[28] or ring-closing metathesis.[29] The olefin has been constructed by various methods including Horner–Wadsworth–Emmons and Wittig olefinations[23,28] and a photochemical rearrangement of an epoxydiazomethyl ketone.[25] The C4-stereocenter has been established via a Sharpless asymmetric epoxidation[25,29] or derived from the chiral pool.[22,26] The C11-stereocenter has been constructed via a Jacobsen kinetic resolution,[23] CBS-reduction,[28] ring opening of (*R*)-propylene oxide,[25] or other chiral pool sources.[22]

Our disconnections of (+)-patulolide C (**1**) are presented in Scheme 4 and make use of the AHF/Wittig olefination tandem reaction. (+)-Patulolide C (**1**) would be accessed via hydrolysis of the C4 acetate in **5**. We envisioned the macro-lactone being formed via an intramolecular Wittig olefination of the stabilized ylide generated in situ from attack of the C11 hydroxyl (patulolide numbering) of α-acetoxy aldehyde **6** on the electrophilic C1 carbon of the Bestmann ketenylidene **7**.[30] Aldehyde **6** would be generated via Rh(I)-catalyzed AHF of C4–C5 *Z*-enol acetate derived from the known alkyne **8**[31] via Rh(I)-catalyzed hydroacetoxylation.[17] The C11 hydroxyl stereocenter in known alkyne **8**[31] is obtained from commercial (*R*)-propylene oxide.

In the event (Scheme 5), alkyne **8**[31] underwent hydroacetoxylation with 1 mol % of $[RhCl(COD)]_2$, 2 mol % of 2-((diphenylphosphino)methyl)pyridine, and AcOH in THF at 110 °C in a sealed tube with excellent stereoselectivity (97%*Z*) to give *Z*-enol acetate **9** in 82% yield. Rh(I)-catalyzed AHF with (*S,S,S*)-BDP proceeded with outstanding regio- and diaster-

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

Scheme 5. Synthesis of (+)-Patulolide C (1)



eoselectivity to produce α-acetoxyaldehyde **6** as the sole product by ^{1}H NMR (in equilibrium with its hemiacetal).

Without isolation, α-acetoxy aldehyde **6** was diluted with toluene and slowly added to a toluene solution of the Bestmann ylide **7**[30] heated to reflux. The nucleophilic attack of the C11 hydroxyl on the electrophilic carbon of the ketene generated the stabilized phosphorus ylide in situ, which underwent an intramolecular Wittig olefination to close the macrocycle and produce patulolide C acetate (**5**) in 62% isolated yield (95% *E*) from *Z*-enol acetate **9**. Note that macrolactonizations are typically done from ω−hydroxy acids, requiring carboxylic acid activation and a net dehydration.[32] These features are built into the reactive Bestmann ylide (**7**), highlighting its utility. This allowed the establishment of the 12-membered lactone with the incorporation of the C1-carbonyl and C2-carbon with great efficiency, while setting the *E*-olefin with excellent selectivity (only *E*-olefin observed by ^{1}H NMR).

Several chemical methods (K_2CO_3/MeOH, Et_3N/MeOH, LiOH/H_2O/THF, guanidine/guanidinium acetate/EtOH) were attempted to remove the acetate while leaving the lactone intact; however, all of these methods showed poor selectivity. An attractive alternative with potentially high selectivity was available in enzymatic ester hydrolysis.[33] Gratifyingly, lipase from *Pseudomonas fluorescens* catalyzed the hydrolysis of the acetate while leaving the lactone untouched, producing (+)-patulolide C (**1**) in quantitative yield (Scheme 5). The diastereomeric ratio (dr) of the final product was measured via HPLC to be 96.6:3.4, indicating a highly diastereoselective AHF and no substantial deterioration of dr in subsequent transformations.[11,12] To illustrate the efficiency of this AHF-based synthesis strategy, a comparison with other published syntheses of patulolide C is warranted. Summaries of step-counts (longest linear sequence LLS), overall % yield, and key reactions for those syntheses are presented in Table 1.

Having demonstrated a successful AHF/intramolecular Wittig macrocyclization cascade in the synthesis of (+)-patulolide (**1**),[12] we next set out to develop and apply an AHF/intermolecular Wittig olefinations for the syntheses of (−)-pyrenophorol (**2**) and (+)-decarestrictine L (**3**) (Figure 2).

Synthesis of (−)-Pyrenophorol (2). (−)-Pyrenophorol (**2**, Figure 2) was first isolated from the plant fungus *Byssachlamys nivea* in 1969 and from culture filtrates of *Stemphylium radicinum*

Table 1. Syntheses of Patulolide C (1)

author, year	steps (LLS)	overall yield (%)	key reaction(s)
Irie,[22] 1992[b]	13	4.2	Yamaguchi macrolactonization
Zwanenburg,[25] 1993[b]	18	0.97	rearrangement of diazomethyl ketone
Takano,[26] 1994[b]	19	2.0	C_2-symmetric bis-epoxide
Sabitha,[23] 2010	14	2.1	α-aminooxylation/HWE olefination
Thomas,[24] 2012[a]	15	3.8	diastereoselective aldehyde allylation
Hase,[27] 1999[a]	8	10	Mitsunobu cyclization
Shibasaki,[28] 2003[b]	9	38	asymm cyanation−ethoxycarbonylation
Sharma,[29] 2008	16	3.4	Grubbs II RCM
Mori,[21] 1988	9	21	Yamaguchi macrolactonization
this work	3 (5)	49 (23)	hydroacetoxylation, AHF, Wittig

[a]Racemic synthesis. [b]Step-count and yield from starting materials not commercially available; (*xy*) yield from commercial reactants.

two years later.[34,35] This natural product is a 16-membered C_2-symmetric macrodiolide containing six stereogenic elements, including two *E*-α,β-unsaturated esters. It has been shown to have antifungal and anthelmintic properties[36] and is the subject of a recent patent application for potential herbicidal use.[37,38] (−)-Pyrenophorol (**2**) has been the target of several total syntheses illustrating a variety of synthetic strategies, which are briefly summarized in Table 2.[39−46]

Table 2. Previous Syntheses of (−)-Pyrenophorol (2)

name, year	steps (LLS)	overall % yield	key reaction(s)
Ohshiro,[39] 1986[a]	8	1	Mitsunobu esterification
Zwanenburg,[40] 1991[b]	11	6.5	asymmetric epoxidation
Kibayashi,[41] 1993[b]	14	11	sulfoxide pyrolysis
Le Floch,[42] 1997[b]	14	4.5	CBS reduction, Wittig olefination
Yadav,[43] 2009	15	3.8	Jacobsen kinetic resolution
Kang,[44] 2011	11	1.6	Yamaguchi esterification
Yadav,[45] 2012	16	8.2	olefin metathesis
Nuguri,[46] 2013[c]	13	2.9	Sharpless epoxidation
this work	5 (7)	32 (19)	Hydroacetoxylation, AHF, Wittig

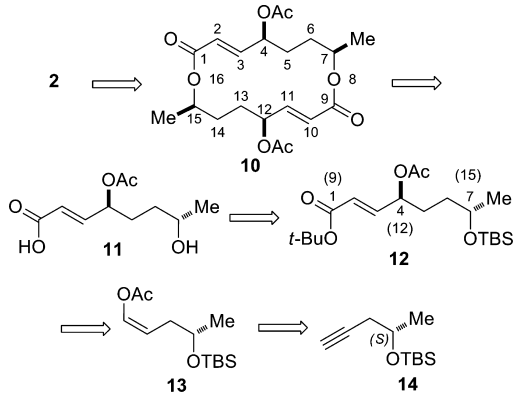
[a]Racemic synthesis. [b]Step-count and yield from starting materials not commercially available; (*xy*) yield from commercial reactants. [c]Enantiomeric synthesis.

Most of the syntheses use the chiral pool for the methyl-bearing stereocenters. The ester functionality has been used in the dimerization step in all of the syntheses, except for Le Floch who used sequential Wittig olefinations for macrocycle formation. The hydroxyl-bearing stereocenters have been set by asymmetric epoxidation,[40] carbonyl α-hydroxylation,[43] CBS reduction,[42] Jacobsen kinetic resolution,[43,46] or Sharpless asymmetric epoxidation[40,45,46] or obtained from the chiral pool.[45,40,42,44] The *E*-olefins have been established via Wittig olefination,[44,42] Horner−Wadsworth−Emmons olefination,[43] sulfoxide pyrolysis,[41] and cross-metathesis.[45]

In the context of (−)-pyrenophorol **2**, we envisioned **2** arising from a double deacetylation of bis-acetate **10** (Scheme 6). The C_2-symmetric macrodiolide **10** could be attained from a head-to-tail Mitsunobu dimerization of the hydroxy acid **11**, which would

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

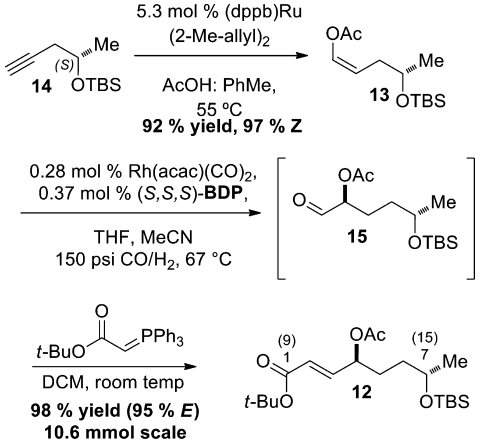
Scheme 6. Synthesis Strategy for (−)-Pyrenophorol (2)



be unmasked from (7,15)-siloxy-*tert*-butyl ester **12**. The γ-acetoxy-α,β-unsaturated ester **12** would be formed via an AHF/Wittig olefination tandem reaction of substrate *Z*-enol acetate **13**, which would be accessed from a Ru(II)-catalyzed hydroacetoxylation[47,48] of known alkyne **14**.[49] The (*S*)-stereocenter in alkyne **14** is obtained from commercial (*S*)-propylene oxide.

Ru(II)-catalyzed hydroacetoxylation[47,48] of known alkyne **14**[49] produced *Z*-enol acetate **13** in 92% yield with excellent stereoselectivity (97% *Z*) (Scheme 7). While the Rh(I) catalyst[17]

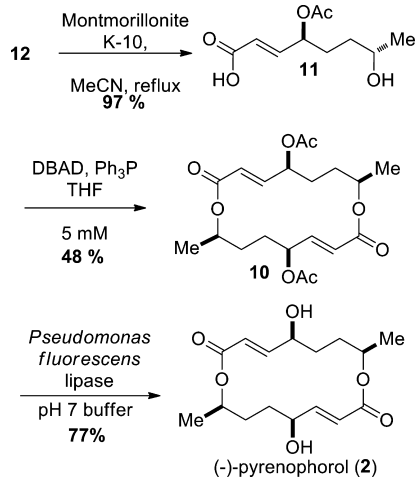
Scheme 7. Hydroacetoxylation/AHF/Wittig Olefination Sequence for Pyrenophorol



worked well in the patulolide C (**1**) synthesis, we found that alkyne **14** decomposed under these conditions. However, the Ru(II)-catalyst[47,48] worked well on alkyne **14** as long as the hydroxyl was protected. Rh(I)-catalyzed AHF, with very low catalyst loading (0.28 mol %), afforded α-acetoxy aldehyde **15** as the sole product by ^{1}H NMR. Without isolation, direct Wittig olefination with *tert*-butyl (triphenylphosphoranylidene) acetate was effected yielding the α,β-unsaturated *tert*-butyl ester **12** in 98% yield with outstanding stereoselectivity (95% *E*). Analysis of the desilylated *tert*-butyl ester via HPLC showed excellent diastereoselectivity (95:5) for the AHF and no erosion of dr during the Wittig olefination.[11,12]

Simultaneous deprotection of both the TBS ether and *tert*-butyl ester was effected with Montmorillonite K-10 clay[50] in refluxing MeCN to give hydroxy acid **11** in 97% yield (Scheme 8). Head-to-tail Mitsunobu dimerization[51] of the hydroxy acid **11** afforded diacetylpyrenophorol **10** in 48% yield. Suppression of higher oligomer formation was ensured by slow addition of

Scheme 8. Synthesis of (−)-Pyrenophorol (2)



hydroxy acid **11** to a solution of di-*tert*-butylazodicarboxylate (DBAD) and Ph_3P at 5 mM concentration. Enzymatic hydrolysis of the acetates with *Pseudomonas fluorescens* lipase under neutral conditions[12] produced (−)-pyrenophorol (**2**) in 77% yield.

Comparison with the prior efforts in Table 2 shows that the AHF-based synthesis described here is substantially shorter and higher yielding than the established benchmarks.

Synthesis of (+)-Decarestrictine L. (+)-Decarestrictine L (**3**), isolated in 1992 from the culture broth of *Penicillium simplicissimum*,[52] is a member of the decarestrictine family of natural products. (+)-decarestrictine L (**3**) has been shown to inhibit cholesterol biosynthesis.[53,54] Numerous syntheses of **3** have been accomplished to date, illustrating a variety of synthetic tactics and strategies summarized in Table 3.[55−64] The majority

Table 3. Previous Syntheses of (+)-Decarestrictine L (3)

name, year	steps (LLS)	overall % yield	key reaction(s)
Kibayashi,[55] 1993[b]	10	2.3	oxa-Michael
Clark,[56] 1994[ab]	9	5.5	carbenoid insertion, ylide rearrangement
Nokami,[57] 1995	7	11	sulfinyl anion addn, [2,3] rearrangement
Carreno,[58] 1998	18	16	α-hydroxy ketone reduction
Hatakeyama,[59] 2000	20	10	Sharpless dihydroxylation
Donaldson,[60] 2003	13	6.3	stereoselective axial methylation
Clark,[61] 2006	10	10	oxonium ylide rearrangement
Fall,[62] 2006	12	21	singlet O_2 furan oxidation
Sudalai,[63] 2009	7	22	D-proline-catalyzed α-aminooxylation
Fall,[64] 2010	10	4.8	stereoselective Michael
this work	4 (6)	47 (27)	AHF, Wittig

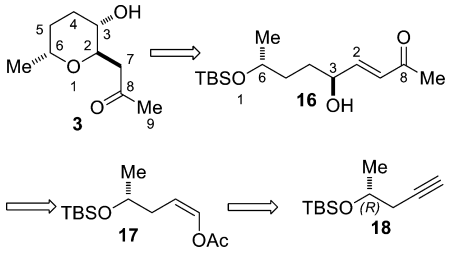
[a]Racemic synthesis. [b]Step-count and yield from starting materials not commercially available; (*xy*) yield from commercial reactants.

of the syntheses use the chiral pool for at least one stereocenter,[55,57,58,60−62,64] and a common strategy for tetrahydropyran (THP) formation has been oxa-Michael addition to an α,β-unsaturated carbonyl.[55,57,63]

A straightforward extension of these considerations to (+)-decarestrictine L (**3**) from the enantiomer of the pyrenophorol starting material **14** is outlined in Scheme 9. We

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

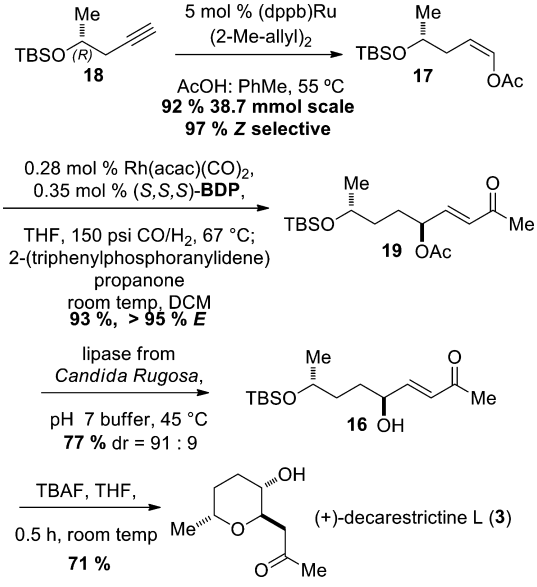
Scheme 9. Synthesis Strategy for (+)-Decarestrictine L (3)



chose the precedented TBAF-mediated desilylation/oxa-Michael cascade of enone **16** for tetrahydropyran formation, suggesting an AHF/Wittig olefination of *Z*-enol acetate **17** followed by deacetylation to yield **16**. AHF substrate **17** would arise via Ru(II)-catalyzed hydroacetoxylation[47,48] of the (*R*)-siloxy alkyne **18**.[49]

Ru(II)-catalyzed hydroacetoxylation[47,48] of the known (4*R*)-(*tert*-butyldimethylsiloxy)-1-pentyne (**18**, Scheme 10)[49] proceeded well on a large scale, producing *Z*-enol acetate **17** in excellent yield (92%, 97% *Z*, 38.7 mmol scale). Utilizing 0.28 mol % of Rh(I) catalyst, the AHF/Wittig olefination of **17** proceeded in 93% yield (>95% *E*) to furnish γ-acetoxy-α,β-unsaturated ketone **19**. In contrast to deacetylation of **10**, attempted acetate hydrolysis of **19** with *Pseudomonas fluorescens* lipase was slow and low yielding, and chemical methods gave complex mixtures with low yields of desired product. Deacetylation was successfully accomplished with lipase from *Candidia Rugosa* affording the γ-hydroxy-α,β-unsaturated ketone **16** in 77% yield. The diastereomeric ratio of **16** was determined to be 91:9 by HPLC analysis. Finally, the TBAF-mediated desilylation/oxa-Michael[63] cyclization cascade afforded (+)-decarestrictine L (**3**) in 71% yield as a single diastereomer after chromatography.

Scheme 10. Synthesis of (+)-Decarestrictine L (3)



Synthesis of (+)-Prelog−Djerassi Lactone. To supplement the AHF/Wittig olefination tandem reactions described thus far, we turned our attention to an AHF/crotylation sequence. We planned on developing and applying this tandem sequence in the context of synthesizing the Prelog−Djerassi lactone (**4**), which has served as a touchstone molecule for showcasing many synthetic methods for polypropionate synthesis. Over 30 different syntheses of the PD lactone (**4**) have been recorded, and the most recent of these are summarized in Table 4.[65−74]

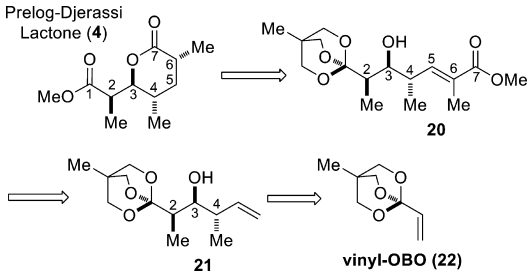
Table 4. Previous Synthesis of PD Lactone (4) since 1990

name, year	steps (LLS)	overall % yield	key reaction(s)
Santelli,[70] 1994[a,b]	10	9.1	diastereoselective ketone crotylation
Irie,[73] 1992[b]	6	40	methylation of γ,δ-epoxy acrylate
Pilli,[74] 1996	8	30	Evans aldol
Campagne,[66] 2001	4	16	asymmetric vinylogous aldol
Santelli,[72] 1990[b]	8	41	Baeyer−Villager
Oppolzer,[69] 1997	8	17	chiral sultam boron aldol
Parsons,[68] 1998[b]	14	12	Ireland−Claisen rearrangement
Fleming,[67] 1998[a]	27	0.98	silyl cuprate SN2′
Santelli,[71] 1993[b]	6	56	dienolate Carroll rearrangement
this work	4 (6)	62 (37)	AHF, crotylation

[a]Racemic synthesis. [b]Step-count and yield from starting materials not commercially available; (*xy*) yield from commercial reactants.

The synthesis strategy for **4** is shown in Scheme 11. The C2 stereochemistry would be established via an AHF of a masked acrylate, followed by a substrate controlled crotylation of the aldehyde to set C3 and C4 in the requisite C2−C3 syn, C3−C4 anti relationship, as shown in homoallylic alcohol **21**. The C6 methyl as well as the C7 carbonyl would be incorporated via an ozonolysis/Wittig tandem to afford α,β-unsaturated ester **20**. Finally, a hydroxyl-directed cationic Rh(I)-catalyzed asymmetric hydrogenation[75] would set the C6 stereochemistry, which would be followed by unmasking of the ortho ester and lactonization to complete the synthesis of PD lactone (**4**).

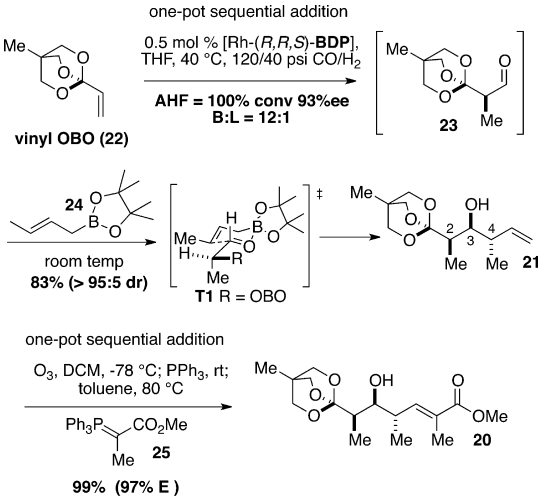
Scheme 11. Synthesis Strategy for PD Lactone (4)



Obviously, the ultimate C1 ester could not be in place during the AHF because the formed stereocenter would be labile in the 1,3-dicarbonyl unit. We sought an acrylate ester equivalent that would bring in the C1 carbon at the ester oxidation state and have a desirable influence on the substrate-controlled crotylation once the AHF was complete. The 1-vinyl-4-methyl-2,6,7-trioxabicyclo [2.2.2]octane ortho ester (vinyl-OBO **22**, Scheme 12) developed by Corey[76] was a prudent choice. Vinyl OBO **22** underwent AHF with [Rh-(*R*,*R*,*S*)-BDP] with good regio- and enantioselectivity to produce α-methyl chiral aldehyde **23** (12:1 B:L, 93% ee, Scheme 12). Once the AHF was complete the syngas was vented and *trans*-2-butenyl pinacolato boronic ester **24** was added at room temperature. The substrate controlled crotylation proceeded with excellent Felkin−Anh selectivity (>95:5 dr), as

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

Scheme 12. AHF/Crotylation and Ozonolysis/Wittig Olefination



depicted in the Zimmerman−Traxler transition state T1,[77] to afford the 2,3-*syn*-3,4-antihomoallylic alcohol **21** in 83% yield. This AHF/crotylation tandem sequence effectively combined catalyst and substrate controlled reactions to set all three stereocenters in a single pot. Homoallylic alcohol **21** was subjected to ozonolysis/Wittig olefination with ylide **25** to produce *α,β*-unsaturated methyl ester **20** in quantitative yield with excellent (97%) *E*-selectivity.

Cationic Rh(I)- and Ir(I)-catalyzed, hydroxyl-directed olefin hydrogenations have been shown to transfer chirality in unsaturated esters similar to **20**.[75] We explored (Scheme 13, Table 5) several catalyst systems for the hydrogenation followed by a one-pot conversion of the hydrogenation product to the targeted PD lactone (**4**).

Scheme 13. Directed Hydrogenation/Lactonization/OBO Cleavage

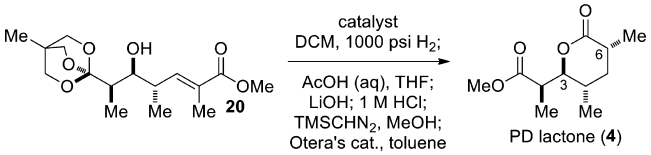


Table 5. Hydrogenation Catalyst Screen

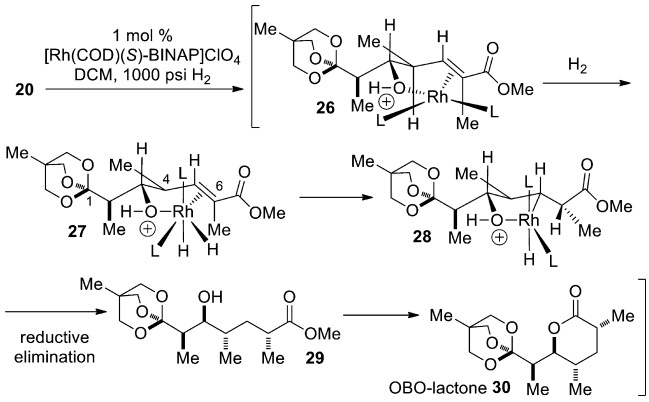
entry	catalyst	% yield[a]	dr(*α*:*β*) for C6-Me[a]
1	10% Pd/C	39	1:1
2	15% [Rh(nbd)(dppb)]BF_4	61	2.5:1
3	0.9% [Ir(pyr)(Cy_3P)]PF_6	66	3:1
4	3% Burgess cat.	63	1.6:1
5	5% [Rh(COD)(*S*)-BINAP]BF_4	30	5:1
6	1% [Rh(COD)(*S*)-BINAP]ClO_4	76	>31:1

[a]Yield and diastereomer ratio measured on **4** before recrystallization; dr determined by comparing integrations of C3-^{12}C—^{1}H minor diastereomer vs ^{13}C—^{1}H satellite of **4** in C_6D_6 at 600 MHz. See the Supporting Information for details.

For a baseline comparison, simple hydrogenation with Pd/C imparted no diastereoselectivity at C6. The cationic Rh(I) catalyst [Rh(nbd)(dppb)]BF_4 gave 2.5:1 mixture of products favoring the desired diastereomer. Although Crabtree's catalyst[78] (entry 3) gave slightly better selectivity (3:1) and Burgess' cationic Ir(I) catalyst[79] (entry 4) gave lower selectivity (1.6:1), all of these results were disappointing in delivering the C6 stereocenter with high selectivity. Incorporating a chiral ligand with the hydroxyl-directed Rh(I)-catalyzed hydrogenation has been shown to increase the diastereoselectivity via double stereodifferentiation.[75] Using [Rh(COD)(*S*)-BINAP]BF_4 afforded a slightly improved 5:1 mixture in favor of the PD lactone (**4**). Vastly superior results were obtained when the noncoordinating perchlorate counterion was incorporated into the catalyst (entry 6), affording a much higher diastereoselectivity (>31:1). Thus, the incorporation of both a chiral (*S*)-BINAP ligand and the perchlorate counterion for the hydroxylation delivered the desired C6 stereocenter with excellent selectivity.

A mechanistic rationale is depicted in Scheme 14 for the observed transfer of chirality. The facial selectivity observed for

Scheme 14



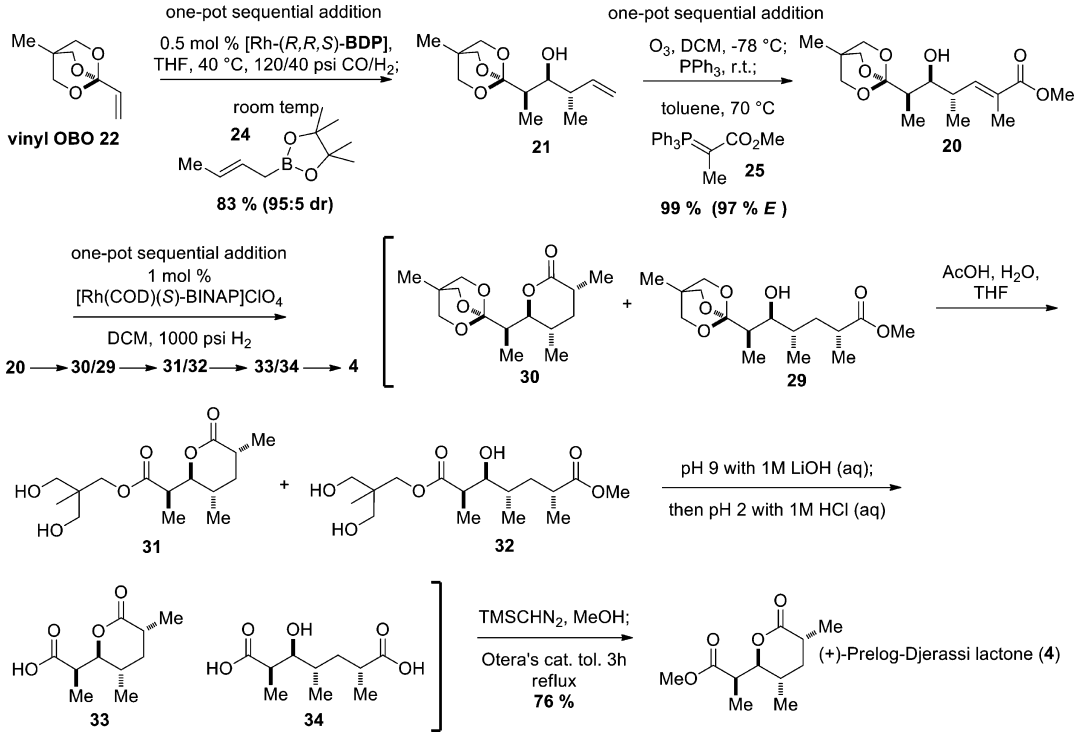
the coordination of the cationic Rh to the hydroxyl group and the electron-deficient alkene in complex **26** allows the methyl and branched, OBO-containing substituents to adopt pseudoequatorial orientations. This facial selectivity is further enforced by the bidentate chiral ligand. Insertion of dihydrogen affords Rh(III) species **27** followed by Rh−H addition across the alkene setting the C6 stereochemistry. Finally reductive elimination produces methyl ester **29**, some of which spontaneously lactonizes to give OBO-lactone **30**.

Following the hydrogenation of **20** to afford OBO-lactone **30** and open chain **29** (Scheme 14), a one-pot conversion to the PD lactone was developed. Although all intermediates **29**−**34** were initially isolated and characterized to establish the details of the transformations, ultimately it was only necessary to do one isolation in the transformation of **20** into the Prelog−Djerassi lactone (**4**). Addition of AcOH catalyzed the decomposition of the OBO-ortho ester to give diol esters **31** and **32**, which upon saponification gave a mixture of **33** and **34**. Esterification of the C1 carboxylic acid with $TMSCHN_2$[80] produced a mixture of **4** and a minor amount of the open chain bis methyl ester that converged to only **4** via neutral lactonization with Otera's catalyst.[81] The conversion of **20** into PD lactone (**4**), requiring only one isolation, proceeded in 76% yield. Overall, the conversion of vinyl OBO **22** into the Prelog−Djerassi lactone (**4**) required only three isolations and was accomplished in 62% overall yield.

Evaluation of the step count and yield efficiencies of this AHF-based approach to this touchstone molecule, with the most recent benchmarks shown in Table 4, illustrates the merits of this alternative route to polyketide-type arrays of stereocenters.

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

Scheme 15. Synthesis of the (+)-Prelog–Djerassi Lactone (4)



CONCLUSION

In summary, four different Rh(I)-catalyzed AHF tandem reactions have been developed and applied using the Landis BDP ligands. We have demonstrated the utility of the alkyne hydroacetoxylation and AHF/Wittig olefination strategy to access γ-hydroxy-α,β-unsaturated carbonyl compounds. A succinct synthesis of (+)-patulolide C (**1**) has been accomplished in three steps from the known alkyne **8** and 49% yield (five steps from commercial material, 23% overall yield).[12] Both Rh(I)-catalyzed hydroacetoxylation and Rh(I)-catalyzed AHF proceeded with excellent selectivity and yield. An in situ reaction of hydroxy aldehyde **6** with the Bestmann ylide **7** generated the stabilized phosphorus ylide, which underwent intramolecular Wittig olefination to give the 12-membered ring lactone **5**, which upon deacetylation afforded (+)-patulolide C (**1**).

A short synthesis of (−)-pyrenophorol (**2**) from the known alkyne **14** has been achieved [five steps, 32% overall yield (seven steps, 19% from commercial material)]. This synthesis features a Ru(II)-catalyzed *Z*-selective alkyne hydroacetoxylation to give **13** followed by an AHF/Wittig olefination to establish the γ-acetoxy-α,β-unsaturated ester motif with high diastereoselectivity. Simultaneous unmasking of both the *tert*-butyl ester and TBS ether unveiled the hydroxy acid **11** required for the Mitsunobu dimerization to give macrodiolide **10**. Finally enzymatic deacetylation afforded (−)-pyrenophorol (**2**) in high diastereomeric purity.

We also applied this strategy to a concise synthesis of (+)-decarestrictine L (**3**), beginning with an anti-Markovnikov hydroacetoxylation of known alkyne **18** to give *Z*-enol acetate **17**. An AHF/Wittig olefination sequence was used to prepare γ-acetoxy-α,β-unsaturated ketone **19** in 93% yield (>95% *E*). After deacetylation to **16**, a TBAF-mediated desilylation/oxa-Michael cascade was utilized to form the trisubstituted THP ring with excellent diastereoselectivity affording (+)-decarestrictine L (**3**) in just four steps and 47% overall yield from **18** (six steps from commercial, 41% overall yield).

Finally an AHF/crotylation tandem sequence was developed and applied in a very short and efficient synthesis of the (+)-Prelog–Djerassi lactone (**4**).[10] This synthesis features an AHF/crotylation tandem reaction of vinyl OBO **22** with the Landis (*R,R,S*)-BDP ligand and *trans*-crotyl boronic acid pinacol ester **24** to produce homoallylic alcohol **21** in 83% yield (>95% dr) setting three of the four required stereocenters in a single pot. Ozonolysis/Wittig homologation with ylide **25** afforded δ-hydroxy-α,β-unsaturated methyl ester **20** in 99% yield (97% *E*). The C6-Me stereocenter was set via a hydroxyl-directed Rh(I)-catalyzed asymmetric hydrogenation with [Rh(COD)(*S*)-BINAP]ClO_4 with excellent diastereoselectivity (>31:1 dr). A one-pot sequence was developed to convert OBO ortho esters **30** and **29** to the PD lactone (**4**). Overall the PD lactone was obtained in 62% yield in just three isolations from vinyl OBO **22** (six steps from commercial, 37% yield).

The step-counts and overall yield efficiencies recorded in these syntheses compare very favorably with prior efforts (Table 6), thus demonstrating the effectiveness of the AHF-initiated tandem strategies employed. Further investigations to develop and apply AHF tandem reactions are underway.

Table 6. Summary Comparison of Synthesis Efficiencies

	AHF tandems		previous syntheses	
target	steps	overall % yield	steps	overall % yield
(+)-patulolide C	3	49	9–19	2–33
(−)-pyrenophorol	5	32	11–16	2–11
(+)-decarestrictine L	4	47	7–20	2–22
(+)-PD lactone	3	62	8–27	1–17

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204–216

EXPERIMENTAL SECTION

General Methods. For moisture-sensitive reactions, toluene and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. THF was also subjected to three freeze−pump−thaw cycles and stored in a nitrogen-filled glovebox prior to use. *trans*-2-Buteny pinacolatoboronic ester (**24**),[84] methyl 2-(triphenylphosphoranylidene)propionate,[85] Otera's catalyst,[81] the Burgess catalyst,[86] [Rh(COD)(*S*)-BINAP]ClO_4,[87] 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester (**22**)[10] (2*R*)-8-nonyn-2-ol,[88] 2-[(diphenylphosphino)methyl]pyridine,[89] (1,4-bis(diphenylphosphino)butane)-Ru(h^3-CH_2MeCH_2)$_2$,[48] and (4*R*) and (4*S*)-(*tert*-butyldimethylsiloxy)-1-pentyne[49] were synthesized according to the reported methods. All other chemicals and lipases were purchased and used as received.

All moisture-sensitive reactions were performed in flame-dried and/or oven-dried glassware under a positive pressure of nitrogen unless otherwise noted. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator at water aspirator pressure. "Dried" refers to addition of ∼1g/mmol anhydrous sodium sulfate followed by filtration.

Analytical thin-layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F_{254} (0.25 mm layer thickness). Visualization was accomplished using UV light and/or a *p*-anisaldehyde (PAA) or $KMnO_4$ charring solution. Flash column chromatography (FCC) was performed on silica gel 60 (230−400 mesh, 60 Å pore size) unless otherwise stated. Solvent mixtures for FCC are reported as $V_1/V_{total} \times 100\%$. Before all compounds containing the OBO ortho ester were subjected to flash column chromatography, the silica gel was deactivated with a 5−10% triethylamine/hexanes, followed by 100% ethyl acetate, then equilibrated with the desired eluent for separation before loading the column with the crude material.

Concentrations (*c*) are reported in g/100 mL. ^{1}H and ^{13}C NMR spectroscopy were recorded at 300 (^{1}H) or 75 (^{13}C) MHz (NSF Grant No. CHE-9208463), 500 (^{1}H) or 125 (^{13}C) and 600 (^{1}H) or 150 (^{13}C) MHz (NIH Grant Nos. P41RR02301 and P41GM66326) as indicated. $CDCl_3$ used for samples containing the OBO ortho ester was flushed through a plug of basic alumina first to remove trace acid. First-order proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept), multiplet (m), apparent (ap), and broad (br). Second-order proton NMR splitting patterns are designated as AB quartet (ABq), ABX pattern (ABX), etc. All coupling constants were rounded to the nearest 0.1 Hz (Hz). High-resolution mass spectra (HRMS) were obtained on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer (NSF Award No. CHE9974839). Exact mass measurements were obtained for all isolated compounds. Supercritical fluid chromatography (SFC) was used with a chiral column (Chiralcel OJ-H) in order to determine enantiomeric excess or UFLC with chiral columns (Chiralcel OJ-H and Chiracel AD-H) in order to determine diastereomeric excess.

(+)-Patulolide C (1). To a 15 mL round-bottom flask equipped with a magnetic stir bar were added patulolide C acetate (**5**) (16.9 mg, 0.066 mmol), *Pseudomonas fluorescens* lipase (PFL) (8.3 mg), and pH 7 aqueous phosphate buffer (0.7 mL). The reaction was allowed to stir at ambient temperature for 3 d, during which time it was monitored by TLC. Upon completion, the product was extracted with diethyl ether (3×), dried, and concentrated. The crude oil was purified via silica gel flash column chromatography to yield (+)-patulolide C (**1**) as a yellow oil (14.0 mg, 99%): IR (neat) 1462, 1647, 1718, 2857, 2932, 3426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.0−1.8 (m, 12H), 1.29 (d, J = 7 Hz, 3H), 4.51 (m, 1H), 5.08 (m, 1H), 6.10 (dd, J = 16, 1 Hz, 1H), 6.85 (dd, J = 16, 7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 20.7, 22.1, 27.8, 28.3, 32.8, 35.9, 70.9, 73.1, 121.5, 149.6, 168.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{21}O_3$ 213.1486, found 213.1480; $[\alpha]_D^{23}$ +4.1 (*c* 0.29 EtOH) [lit.[28] $[\alpha]_D^{23}$ +5.0 (*c* 0.32 EtOH)].

(−)-Pyrenophorol (2). In a 25 mL round-bottom flask containing **10** (24 mg, 0.0605 mmol) were added lipase from *Pseudomonas fluorescens* (185 mg) and 10 mL of phosphate buffer (pH = 7). The reaction was stirred at ambient temperature for 14 days and monitored by TLC. Once complete, the mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate, filtered, and concentrated. The residue was purified via flash column chromatography (40−50% ethyl acetate/hexane) to yield (−)-pyrenophorol (**2**) as clear oil, which solidified on standing (14.6 mg, 77%): IR (neat) 1281, 1647, 2849, 2917, 3442 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.7, 5.1 Hz, 1H), 6.00 (dd, J = 15.7, 1.6 Hz, 1H), 5.20−5.12 (m, 1H), 4.36−4.29 (m, 1H), 2.16 (d, J = 6.5 Hz, 1H), 1.96 m, 1H), 1.86 (m, 1H), 1.77−1.61 (m, 2H), 1.29 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2, 29.0, 30.5, 69.8, 70.4, 122.1, 149.5, 164.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{24}O_6Na$ 335.1466, found 335.1461; $[\alpha]_D^{23}$ = −4.0 (*c* 0.25 acetone); mp 131−133 °C [lit.[36] $[\alpha]_D^{23}$ = −3.2 (*c* 0.25 acetone), mp 136−138 °C]. A sample of the white solid was recrystallized from $Et_2O/CHCl_3$ for X-ray analysis and was in good agreement with the published crystal structure.[36]

(+)-Decarestrictine L (3). To a 100 mL round-bottom flask containing ketone **16** (952 mg, 3.32 mmol), in THF (30 mL) under nitrogen was added TBAF (10 mL, 1 M THF) via an addition funnel dropwise over 10 min. After 30 min of stirring at ambient temperature, the reaction was complete as confirmed by TLC. The reaction was then diluted with ethyl acetate and extracted with NH_4Cl, dried with $MgSO_4$, filtered, and concentrated. The residue was purified via flash column chromatography (50% ethyl acetate: hexane) to yield (+)-decarestrictine L (**3**) as clear colorless oil (404 mg, 71%): IR (neat) 1107, 1543, 1577, 1710, 2970, 3675 (broad OH) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (q, J = 6.4 Hz, 1H), 3.99−3.92 (m, 1H), 3.46−3.36 (m, 1H), 2.74 (d, J = 6.4 Hz, 2H), 2.21 (s, 3H), 2.00 (d, J = 6.6 Hz, 1H), 1.93−1.82 (m, 1H), 1.78−1.66 (m, 2H), 1.63−1.51 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.5, 27.0, 28.2, 30.5, 46.3, 67.4, 69.4, 72.0, 207.6; HRMS (ESI-TOF) m/z $[M + NH_4]^+$ Calcd for $C_9H_{20}O_3N$ 190.1438, found 190.1437; $[\alpha]_D^{23}$ = +30.8 (*c* 0.5 $CHCl_3$) [lit.[52] $[\alpha]_D^{23}$ = +28.8 (*c* 0.5 $CHCl_3$)]. The bromobenzoate of decarestrictine L SI-1 was made and crystallized to afford X-ray quality crystals. This data confirmed the absolute stereochemistry and is reported in the Supporting Information.

(+)-Prelog−Djerassi Lactone (4). In a nitrogen-filled glovebox, *α*,*β*-unsaturated methyl ester **20** (200 mg, 0.636 mmol) was added to a 1.5 dram vial equipped with a magnetic stir bar. To the vial were added [Rh(COD)(*S*)-BINAP]ClO_4 (6 mg, 0.0064 mmol) and DCM (0.636 mL). The vial was then placed in a 100 mL Parr Bomb stainless steel reactor. The reactor was sealed and placed behind a blast shield on top of a stir plate. The reactor was charged with 1000 psi H_2 and stirred for 48 h. The pressure was vented to atmosphere and the vial removed from the Parr bomb. The reaction was concentrated and then dissolved in THF/H_2O (7.7:1.3 mL), and 2 drops of AcOH was added. The mixture was stirred for 1 h then basified with 1 M LiOH to a pH = 10 and stirred for 1 h. Then the reaction was acidified to pH = 2 with 1 M HCl and extracted five times with ethyl acetate, dried, and concentrated. The residue was then dissolved in methanol, and $TMSCHN_2$ (6 mL, 2.0 M Et_2O) was added. The mixture was stirred for 30 min and concentrated. The residue was then dissolved in toluene (5 mL), and Otera's catalyst (14 mg, 0.013 mmol) was added. The flask was fitted with a reflux condenser and heated to reflux for 4 h, cooled to ambient temperature, and concentrated. The residue was purified via FCC (1:1 Et_2O: pentane) to obtain (+)-Prelog−Djerassi lactone (**4**) as a white solid which was recrystallized from pentane to white needles (103.4 mg, 76%): R_f = 0.22, 50% diethyl ether/hexanes; IR (neat) 1180, 1209, 1446, 1730, 2877, 2932, 3004, 3427, 3456 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.54 (dd, J = 10.5, 2.9 Hz, 1H), 3.73 (s, 3H), 2.73 (qd, J = 7.1, 2.6 Hz, 1H), 2.50 (ddq, (ap. sept.) J = 13.6, 7.0, 7.0, 1H), 1.99−1.86 (m, 2H), 1.42 (td, (ap. q.) J = 13.1, 12.1 Hz, 1H), 1.29 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 173.3, 86.2, 52.2, 41.3, 37.3, 36.2, 30.9, 17.2, 17.0, 8.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{18}O_4Na$ 237.1098, found 237.1096; mp 76−77 °C (lit.[82] 77.0−77.5 °C); $[\alpha]_D^{23}$ = +39.0 (*c* 0.2 $CHCl_3$) [lit.[82] $[\alpha]_D^{23}$ = +39.0 (*c* 0.2 $CHCl_3$)].

(*R*,*Z*)-8-Hydroxynon-1-en-1-yl Acetate (9). All reagents were combined in a nitrogen-filled glovebox. To a 15 mL pressure tube (25.4 mm o.d. × 10.2 cm long rated to 150 psi) equipped with a stir bar were added alkyne **8** (250 mg, 1.78 mmol), $[Rh(COD)Cl]_2$ (8.8 mg, 0.0178 mmol), 2-[(diphenylphosphino)methyl]pyridine (10 mg, 0.0356

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

mmol), acetic acid (103 mL, 1.78 mmol), and 1.78 mL of THF (degassed). The pressure tube was then fitted with a septum, removed from the glovebox, and purged with argon (outlet needle equipped). After 1−2 min of purging the septum was quickly replaced with a Teflon screw cap fitted with a front-seal O-ring, and tightened by hand. The pressure tube was then placed in a 110 °C oil bath with stirring and the temperature maintained for 24 h. The tube was then removed from the oil bath and allowed to cool to ambient temperature. The mixture was then filtered through a 1-in. silica plug and rinsed thoroughly with ethyl acetate. The filtrate was concentrated to give a crude oil, which was purified by silica gel flash column chromatography (10% ethyl acetate: hexanes) to yield 292.3 mg of hydroxy-*Z*-enol acetate **9** as a yellow oil (82% yield). Kugelrohr distillation (0.1 mmHg, 120 °C) provided a clear, colorless oil: IR (neat) 1062, 1221, 1369, 1671, 1757, 2858, 2931, 3386 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 6 Hz, 3H), 1.26−1.49 (m, 9H), 2.11−2.17 (m, 2H), 2.15 (s, 3H), 3.75−3.85 (m, 1H), 4.86 (dt, J = 6, 8 Hz, 1H), 7.00 (dt, J = 6, 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 23.8, 24.5, 25.7, 29.3, 29.3, 39.5, 68.3, 114.4, 134.3, 168.5; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{20}O_3Na$ 223.1305, found 223.1303; $[\alpha]_D^{23}$ −3.14 (c 1.02, $CHCl_3$) (98% ee from epoxide).

(5*S*,12*R*,*E*)-12-Methyl-2-oxooxacyclododec-3-en-5-yl Acetate (5). All reagents were combined in a nitrogen- filled glovebox. To a 48 mL pressure tube (38.1 mm o.d. × 10.2 cm long rated to 150 psi from Ace Glass, Inc.) equipped with a stir bar were added **9** (203 mg, 1.01 mmol), $Rh(acac)(CO)_2$ (3 mg, 0.01 mmol), (*S*,*S*,*S*)-**BDP** (26 mg, 0.02 mmol), and 1 mL of THF. The pressure tube was then connected to a gauged pressure reactor assembly and removed from the glovebox. The pressure tube was purged five times with syngas (1:1 CO/H_2) and then charged to 150 psi. A blast shield was placed in front of the reactor for safety. The reaction tube was submerged in a 50 °C oil bath with stirring and allowed to react for 24 h. The pressure tube was removed from the oil bath and allowed to reach ambient temperature and the pressure was vented to 20 psi. The reactor was equipped with an argon inlet and the remaining syngas was vented through the Schlenk line. A small aliquot was removed from the reaction to confirm >95% consumption of **9** by ^1H NMR.

The above solution of aldehyde **6** was diluted with toluene (9 mL) and a 0.5 mL (0.05 mmol) sample was removed and diluted with toluene (to 50 mL). This solution was slowly added via syringe pump to a refluxing toluene solution (450 mL) of (triphenylphosphoranylidene)-ketene (91 mg, 0.3 mmol) over 20 h. The reaction was allowed to reflux for an additional 1 h and then cooled to ambient temperature. The crude reaction was concentrated and purified via silica gel flash column chromatography (5% ethyl acetate/hexanes) to yield **5** as a yellow oil (7.9 mg, 62%): IR (neat) 1462, 1651, 1722, 1743, 2863, 2937 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06−1.82 (m, 12H), 1.29 (d, J = 7 Hz, 3H), 2.08 (s, 3H), 5.08 (m, 1H), 5.41 (m, 1H), 6.06 (dd, J = 16, 1 Hz, 1H), 6.83 (dd, J = 16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.1, 21.3, 22.3, 27.7, 28.1, 32.9, 33.1, 72.8, 73.2, 122.6, 145.6, 167.2, 169.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{22}O_4Na$ 277.1411, found 277.1406; $[\alpha]_D^{23}$ −5.3 (c 0.57 EtOH).

(*S*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-1-yl Acetate (13). In a nitrogen-filled glovebox, (4*S*)-4-(*tert*-butyldimethylsiloxy)-1-pentyne (**14**) (11.68 g, 58.9 mmol) was added to a 50 mL pressure tube containing a stir bar. To the same flask were added (1,4-bis(diphenylphosphino)butane)Ru(η^3-2-Me-allyl)$_2$ (2.0 g, 3.14 mmol), acetic acid (10 mL), and toluene (9 mL). The tube was fitted with a rubber septum and removed from the glovebox. The headspace of the tube was flushed with argon for 3 min; the septum was replaced with a threaded Teflon stopper and heated in an oil bath for 40 h. The reaction was cooled to ambient temperature and concentrated. The residue was purified via flash column chromatography (2−5% diethyl ether/hexane) to afford **13** as clear colorless oil (14.05 g, 92%, 97% *Z* selectivity by ^1H NMR): R_f = 0.5 (10% diethyl ether/hexane); IR (neat) 1056, 1087, 1134, 1221, 1368, 1473, 1673, 1761, 2858, 2896, 2930, 2958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, J = 6.5, 1.5 Hz, 1H), 4.93 (td, J = 7.6, 6.5 Hz, 1H), 3.85 (h, J = 6.1 Hz, 1H), 2.34−2.21 (m, 2H), 2.14 (s, 3H), 1.14 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.8, −4.6, 18.2, 20.8, 23.4, 25.9, 34.6, 68.0, 110.4, 135.0, 168.1; HRMS (ESI-TOF) m/z $[M + NH_4]^+$ calcd for $C_{13}H_{30}O_3SiN$ 276.1990, found 276.1980; $[\alpha]_D^{23}$ = −2.2 (c 1.0 $CHCl_3$).

(4*S*,7*S*,*E*)-*tert*-Butyl 4-Acetoxy-7-((*tert*-butyldimethylsilyl)-oxy)oct-2-enoate (12). In a nitrogen-filled glovebox, a 300 mL pressure tube with a stir bar was charged with *Z*-enol acetate **13** (2.74 g, 10.6 mmol), (acetylacetonato)dicarbonylrhodium (7.2 mg, 0.028 mmol), (*S*,*S*,*S*)-bisdiazaphospholane (61 mg, 0.047 mmol), acetonitrile (1.3 mL), and tetrahydrofuran (1.5 mL). The reaction vessel was fitted with a pressure head and removed from the glovebox. It was filled/purged 5 times with syngas (150 to 40 psi) and then pressurized to 150 psi and placed in a 67 °C oil bath with vigorous stirring behind a blast shield. After 24 h 10 psi of syngas had been consumed, and the vessel was pressurized to 150 psi and allowed to react another 23 h. The vessel was then cooled to ambient temperature and the pressure vented down to 20 psi. An aliquot was removed via syringe through the top septum and concentrated for NMR analysis. This aliquot showed complete conversion to the branched aldehyde **15**; it was then purified via flash column chromatography (10% ethyl acetate: hexanes) for full characterization. The data are presented below. The remaining reaction mixture was then fully vented through an argon Schlenk line and the pressure head removed and replaced with a rubber stopper and argon needle. To the reaction vessel were added *tert*-butyl 2-(triphenylphosphoranylidene) acetate (6 g, 15.9 mmol) and dichloromethane (6 mL) and stirred for 3 h. The reaction was monitored by TLC, and when complete (3 h), it was concentrated and purified via flash column chromatography (3−5% diethyl ether/hexane) to afford **12** as clear colorless oil (4.02 g, 98%, 96% *E*): IR (neat) 1155, 1314, 1369, 1463, 1472, 1662, 1719, 1746, 2858, 2931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (dd, J = 15.7, 5.6 Hz, 1H), 5.85 (dd, J = 15.7, 1.5 Hz, 1H), 5.37 (q, J = 5.6 Hz, 1H), 3.79 (h, J = 6.1 Hz, 1H), 2.09 (s, 3H), 1.83−1.71 (m, 1H), 1.70−1.58 (m, 1H), 1.48 (s, 9H), 1.44 (m, 2H), 1.12 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.8, −4.4, 18.1, 21.1, 23.7, 25.9, 28.1, 29.9, 34.7, 68.1, 72.6, 80.7, 123.5, 144.0, 165.3, 170.11; HRMS (ESI-TOF) m/z $[M + NH_4]^+$ Calcd for $C_{20}H_{42}O_5SiN$ 404.2827, found 404.2827; $[\alpha]_D^{23}$ = −3.5 (c 1.04 $CHCl_3$).

(2*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-acetoxyhexanal (15): IR (neat) 776, 836, 897, 1055, 1251, 1374, 1469, 1744, 2855, 2929, 2957, 3465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 4.99 (dd, J = 8.4, 4.7 Hz, 1H), 3.82 (h, J = 6.0 Hz, 1H), 2.18 (s, 3H), 1.97 (m, 1H), 1.76−1.65 (m, 1H), 1.52 (m, 2H), 1.14 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.8, −4.4, 18.1, 20.6, 23.6, 24.9, 25.8, 34.6, 67.9, 78.4, 170.6, 198.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{29}O_4Si$ 289.1830, found 289.1836; $[\alpha]_D^{23}$ = −4.2 (c 0.48 $CHCl_3$).

(4*S*,7*S*,*E*)-4-Acetoxy-7-hydroxyoct-2-enoic Acid (11). To a 100 mL round-bottom flask were added **12** (268 mg, 0.69 mmol), Montmorillonite K-10 (138 mg), and acetonitrile (69 mL). The flask was fitted with a reflux condenser and refluxed for 24 h. The reaction was cooled to ambient temperature and filtered through a pad of Celite, and the solids were washed with ethyl acetate. The filtrate was concentrated to give viscous oil, which was purified via flash column chromatography (5% methanol/94% dichloromethane/1% acetic acid) to afford the hydroxy acid **11** as viscous oil (145 mg, 97%): IR (neat) 982, 1027, 1237, 1375, 1662, 1718, 2930, 2967, 3421(broad) cm^{-1}; ^1H NMR (400 MHz, methanol-d_4) δ 6.84 (dd, J = 15.7, 5.3 Hz, 1H), 5.91 (dd, J = 15.8, 1.6 Hz, 1H), 5.40 (dtd, J = 7.1, 5.4, 1.6 Hz, 1H), 3.77−3.67 (m, 1H), 2.10 (s, 3H), 1.91−1.80 (m, 1H), 1.69 (m, 1H), 1.55−1.38 (m, 2H), 1.16 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, MeOH-d4) δ 20.8, 23.5, 31.2, 35.3, 49.0, 68.2, 74.0, 122.8, 147.1, 169.2, 171.8; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{10}H_{15}O_5$ 215.0924, found 215.0919; $[\alpha]_D^{23}$ = −3.2 (c 0.5 MeOH).

(2*R*,5*S*,6*E*,10*R*,13*S*,14*E*)-2,10-Dimethyl-8,16-dioxo-1,9-dioxacyclohexadeca-6,14-diene-5,13-diyl Diacetate (10). To a 100 mL round-bottom flask was added hydroxy acid **11** (282 mg, 1.31 mmol) and this oil was azeotropically dried with toluene 7 times and then placed under argon. To an oven-dried 500 mL round-bottom flask under argon were added THF (234 mL), triphenylphosphine (1.72 g, 6.55 mmol), and di-*tert*-butyl azodicarboxylate (1.51 g, 6.55 mmol). Hydroxy acid **11** was dissolved in 28 mL of THF and added to the reaction flask slowly via

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

syringe pump over 6 h. The reaction was stirred for an additional 1 h and then concentrated on a rotovap. The residue was dissolved in dichloromethane (50 mL), and trifluoroacetic acid (5 mL) was added and stirred for 3 h. The reaction mixture was then extracted with sodium bicarbonate, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified via flash column chromatography (15% ethyl acetate: hexane) to afford **10** a clear oil which solidified upon standing (126 mg, 48%): IR (neat) 1021, 1233, 1281, 1376, 1653, 1709, 1740, 2876, 2956, 2992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, J = 15.8, 6.8 Hz, 1H), 5.98 (dd, J = 15.8, 1.1 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 1H), 2.08 (s, 3H), 1.93−1.79 (m, 2H), 1.79−1.68 (m, 1H), 1.67−1.57 (m, 1H), 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.5, 21.1, 27.9, 28.7, 69.8, 72.1, 124.2, 143.7, 164.8, 169.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{28}O_8Na$ 419.1677, found 419.1677; $[\alpha]_D^{23}$ = −33.2 (c 0.47 $CHCl_3$); mp 119−120 °C.

(*R*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-1-yl Acetate (17). In a nitrogen-filled glovebox, (4*R*)-4-(*tert*-butyldimethylsiloxy)-1-pentyne (**18**) (7.68 g, 38.7 mmol) was added to a 100 mL round-bottom flask containing a stir bar. To the same flask were added (1,4-bis(diphenylphosphino)butane)Ru(η^3-2-Me-allyl)$_2$ (1.23 g, 1.96 mmol), acetic acid (9 mL), and toluene (8 mL). The flask was fitted with a rubber septum and removed from the glovebox, placed under N_2, and heated in an oil bath for 16 h. The reaction was cooled to ambient temperature, diluted with ethyl acetate, and extracted with $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was purified via flash column chromatography (2−5% diethyl ether: hexane) to afford **17** as a clear colorless oil (9.23 g, 92%, 97% Z selectivity by NMR): R_f = 0.5 (10% diethyl ether: hexane); IR (neat) 1056, 1220, 1368, 1463, 1473, 1674, 1761, 2858, 2896, 2958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, J = 6.5, 1.5 Hz, 1H), 4.93 (td, J = 7.6, 6.5 Hz, 1H), 3.85 (h, J = 6.1 Hz, 1H), 2.28 (m, 2H), 2.14 (s, 3H), 1.14 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.6, −4.4, 18.3, 20.9, 23.6, 26.0, 34.8, 68.0, 110.6, 135.2, 168.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{26}O_3SiNa$ 281.1544, found 281.1544; $[\alpha]_D^{23}$ = +2.6 (c 1.0 $CHCl_3$).

(5*S*,8*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-oxonon-3-en-5-yl Acetate (19). In a nitrogen-filled glovebox, a 50 mL pressure tube with a stir bar was charged with Z-enol acetate **17** (2.69 g, 10.4 mmol), (acetylacetonato)dicarbonylrhodium (7.5 mg, 0.029 mmol), (*S*,*S*,*S*)-bisdiazaphospholane (48 mg, 0.035 mmol), and tetrahydrofuran (2.5 mL). The reaction vessel was fitted with a pressure head and removed from the glovebox. It was filled/purged 5 times with syngas (150 to 40 psi) and then pressurized to 150 psi and placed in a 67 °C oil bath with vigorous stirring behind a blast shield. After 7 h, 40 psi of syngas had been consumed, and the vessel was pressurized to 150 psi and allowed to react another 40 h. The vessel was then cooled to ambient temperature and the pressure vented down to 20 psi. The reaction mixture was then fully vented through an argon Schlenk line and the pressure head removed and replaced with a rubber stopper and argon needle. To the crude reaction were added 1-(triphenylphosphoranylidene)-2-propanone (5 g, 15.7 mmol) and dichloromethane (2 mL), and the reaction was stirred overnight. The crude reaction was diluted with ether and flushed through a silica plug, concentrated and purified via flash column chromatography (5−8% ethyl acetate: hexane) to afford **19** as a clear colorless oil (3.18 g, 93%, >95% E): IR (neat) 1140, 1233, 1373, 1473, 1636, 1683, 1704, 1743, 2857, 2930, 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65 (dd, J = 16.1, 5.3 Hz, 1H), 6.17 (dd, J = 16.1, 1.5 Hz, 1H), 5.42 (dtd, J = 7.0, 5.4, 1.5 Hz, 1H), 3.86−3.75 (m, 1H), 2.27 (s, 3H), 2.10 (s, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.52−1.37 (m, 2H), 1.12 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.8, −4.3, 18.1, 21.0, 23.7, 25.9, 27.4, 29.8, 34.5, 67.8, 72.4, 130.2, 144.1, 170.1, 198.0; HRMS (ESI-TOF) m/z $[M + NH_4]^+$ calcd for $C_{17}H_{36}O_4SiN$ 346.2409, found 346.2411; $[\alpha]_D^{23}$ = −12 (c 0.2 $CHCl_3$).

(5*S*,8*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxynon-3-en-2-one (16). To a 100 mL round-bottom flask containing ketone **19** (1.416 g, 4.31 mmol) was added lipase from *Candida rugosa* (6 g) and pH = 7 phosphate buffer (30 mL, 0.1 M). The flask was stoppered with plastic cap and placed in a 45 °C oil bath. The reaction was stirred for 32 h and shown to be complete by TLC. The water was removed in vacuo, the brown residue was triturated with ethyl acetate, filtered through Celite, concentrated, and purified via flash column chromatography (30% ethyl acetate/hexane) to afford **16** as a clear colorless oil (959 mg, 77%): IR (neat) 775, 835, 1050, 1139, 1254, 1362, 1677, 2930, 3427 (broad OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, J = 16.0, 4.8 Hz, 1H), 6.30 (dd, J = 16.0, 1.7 Hz, 1H), 4.38−4.32 (m, 1H), 3.90 (m 1H), 2.68 (d, J = 5.1 Hz, 1H), 2.28 (s, 3H), 1.84−1.73 (m, 1H), 1.71−1.51 (m, 3H), 1.16 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.7, −4.4, 18.1, 23.2, 25.9, 27.6, 31.9, 34.3, 68.3, 70.8, 129.2, 149.0, 198.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{30}O_3Si$ 287.2037, found 287.2045; $[\alpha]_D^{23}$ = −6 (c 0.5 $CHCl_3$).

(2*R*,3*S*,4*S*)-4-Methyl-2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)hex-5-en-3-ol (21). All reagents for the AHF were combined in a nitrogen-filled glovebox. To a 300 mL pressure tube equipped with a stir bar were added vinyl-OBO **22** (610 mg, 3.90 mmol), Rh(acac)(CO)$_2$ (5 mg, 0.0194 mmol), (*R*,*R*,*S*)-**BDP** (Bis-[(*R*,*R*,*S*)-DiazaPhos-SPE]) (51 mg, 0.0388 mmol), and 1.94 mL of THF. The pressure tube was then connected to a gauged pressure reactor assembly and removed from the glovebox. A blast shield was placed in front of the vessel for safety. It was filled/purged 5 times with CO (120 to 40 psi) and then pressurized to 80 psi CO. Then it was charged with 80 psi syngas (1:1 CO/H_2) for a total pressure of 160 psi (3:1 CO/H_2). The vessel was then placed in a 40 °C oil bath and stirred for 43 h during which time the pressure dropped to 155 psi. The reaction vessel was then vented in the fume hood down to 20 psi, removed from the oil bath, and allowed to cool to ambient temperature. The remaining pressure was vented into an argon Schlenk line in a fume hood. The pressure head was removed and replaced with a septum. A small aliquot was removed and analyzed by ^1H NMR to confirm completion and obtain an accurate B:L ratio (B:L = 12:1 by ^1H NMR in C_6D_6 RD = 10, 64 scans). Once under argon, the reaction was then transferred to a nitrogen line and *trans*-2-butenylpinacolato boronic ester (**24**) (1.6 mL, 7.8 mmol) was added at rt. The reaction was allowed to stir at ambient temperature for 24 h, transferred to a 100 mL round-bottom flask with methanol, concentrated, and purified via FCC (3−20% ethyl acetate/hexanes) to yield **21** as a clear colorless oil which solidified upon standing (786 mg, 83%): R_f = 0.30, 30% ethyl acetate/hexanes; IR (neat) 1088, 1269, 1310, 1359, 1377, 1411, 1457, 1639, 2885, 2940, 3082, 3539 (broad stretch) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, J = 17.3, 10.3, 7.8 Hz, 1H), 5.08 (ddd, J = 17.2, 1.8, 1.0 Hz, 1H), 5.03 (ddd, J = 10.3, 1.8, 0.7 Hz, 1H), 3.91 (s, 6H), 3.84 (d, J = 9.4 Hz, 1H), 3.06 (s, 1H), 2.22 (sext, J = 7.6 Hz, 1H), 1.96 (qd, J = 7.1, 1.1 Hz, 1H), 0.99 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 114.1, 110.9, 73.4, 72.9, 41.0, 40.8, 30.5, 16.7, 14.7, 6.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{23}O_4$ 243.1591, found 243.1598; mp 41−42 °C; $[\alpha]_D^{23}$ = −29.6 (c 0.5 ethyl acetate).

(4*S*,5*S*,6*R*,*E*)-Methyl 5-Hydroxy-2,4-dimethyl-6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hept-2-enoate (20). To a 100 mL round-bottom flask equipped with a stir bar were added homoallylic alcohol **21** (7.5 g, 30.95 mmol) and DCM (100 mL). The flask was cooled to −78 °C. The solution was then sparged with a stream of ozone until a blue color persisted (about 15 min). Then oxygen was bubbled through the solution until the blue color disappeared. The flask was then charged with triphenylphosphine (16.24 g, 61.9 mmol) and allowed to warm to ambient temperature and stirred overnight. The solvent was removed in vacuo and replaced with toluene (100 mL), and ylide **25** (23.9 g, 68.6 mmol) was added. The mixture was placed in a 70 °C oil bath and allowed to stir for 16 h. The flask was cooled to ambient temperature and concentrated. The residue was purified via FCC (5−30% ethyl acetate/hexanes) to give **20** as a clear colorless oil which solidified upon standing (9.62 g, 91%, >95% E isomer): R_f = 0.20, 30% ethyl acetate/hexanes; IR (neat) 947, 1011, 1055, 1092, 1130, 1190, 1227, 1267, 1318, 1360, 1431, 1457, 1649, 1713, 2338, 2362, 2879, 2929, 3509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (dq, J = 9.6, 1.4 Hz, 1H), 3.97 (d, J = 9.1 Hz, 1H), 3.90 (s, 6H), 3.70 (s, 3H), 3.03 (s, 1H), 2.59 (tq, J = 9.3, 6.9 Hz, 1H), 1.97 (qd, J = 7.2, 1.2 Hz, 1H), 1.87 (d, J = 1.4 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 146.2, 127.2, 110.5, 73.5,

dx.doi.org/10.1021/jo502301k | J. Org. Chem. 2015, 80, 204−216

72.6, 51.6, 40.6, 36.3, 30.3, 16.0, 14.4, 12.7, 6.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{27}O_6$ 315.1803, found 315.1805; mp 98−99 °C; $[\alpha]_D^{23} = -8.4$ (c 0.5 ethyl acetate).

PD Lactone dr Experiment. The determination of the diastereomeric ratio via ^{1}H NMR analysis of the PD lactone (**4**) obtained from the asymmetric hydrogenation/lactonization/OBO cleavage/esterification sequence was performed according to the method of Davies.[83] The sample was purified via flash column chromatography, which did not separate the diastereomers from each other (or enhance the ratio). The ^{1}H NMR was recorded on a 600 MHz spectrometer (no spinning to avoid "spinning sidebands") the sample in C_6D_6 in order to resolve (with baseline separation) the diastereomer peaks as shown in spectra on pages S36 and S37. The pulse delay was set to 17 s (>5T_1, T_1 = 3 s) to ensure complete (>99%) relaxation of all nuclei observed. The number of scans taken was increased to 64 in order to obtain acceptable signal-to-noise ratio (>10:1) for the smallest peak. The diastereomer ratio was calculated with integrations of the ^{13}C−^{1}H (satellite of major diastereomer 4.43 ppm) and the ^{12}C−^{1}H (minor diastereomer 4.24 ppm) according to the equation below. The integrations are divided by 0.0055 (0.01108/2 = 0.0055) in order to account for the ^{13}C natural abundance (1.1%) and using only one of the satellites. The same analysis was performed on the crystals obtained (Supporting Information, S38−S39).

(^{13}C−^{1}H satellite major)/(^{12}C−^{1}H minor)/0.0055 = diast. ratio

1.00/5.82/0.0055 = 31.2:1 (before recrystallization, Supporting Information, S36−S37)

1.00/1.29/0.0055 = 140.9:1 (after recrystallization, Supporting Information, S38−S39)

After recrystallization, both ^{1}H (S34) and ^{13}C NMR (S35) were recorded in $CDCl_3$ (600 MHz) in order to match the reported data (Supporting Information, S49).[82]

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra/comparison tables and HPLC/SFC chromatograms for select compounds and crystallographic data for the 4-bromobenzoyl ester of (+)-decarestrictine L. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: burke@chem.wisc.edu.

Author Contributions

Both A.M.M. and R.M.R. contributed to the syntheses of (−)-pyrenophorol (**2**) and (+)-decarestrictine L (**3**). R.M.R. synthesized (+)-patulolide C (**1**) and (+)-Prelog−Djerassi lactone (**4**).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the support of the UW−Madison Department of Chemistry. We also acknowledge Victor Jaffett for his assistance on (+)-patulolide C. We wish to thank Prof. Clark Landis for helpful discussions, Prof. Jennifer Schomaker for HPLC access, and Dr. Ilia Guzei for X-ray crystallographic confirmation. We also wish to thank Dr. Charlie Fry for assistance with NMR acquisition and interpretation.

■ REFERENCES

(1) Gual, A.; Godard, C.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135−1146.

(2) Horváth, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169−2173.

(3) Reddy, L. V. R.; Kumar, V.; Sagar, R.; Shaw, A. K. *Chem. Rev.* **2013**, *113*, 3605−3631.

(4) Britton, R.; Kang, B. *Nat. Prod. Rep.* **2013**, *30*, 227−236.

(5) Chercheja, S.; Nadakudity, S. K.; Eilbracht, P. *Adv. Synth. Catal.* **2010**, *352*, 637−643.

(6) Stiller, J.; Vorholt, A. J.; Ostrowski, K. A.; Behr, A.; Christmann, M. *Chem.—Eur. J.* **2012**, *18*, 9496−9499.

(7) Chercheja, S.; Rothenbücher, T.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *351*, 339−344.

(8) Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528−531.

(9) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6757−6761.

(10) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 2572−2575.

(11) Wong, G. W.; Landis, C. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1564−1567.

(12) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 1180−1182.

(13) Bellini, R.; Reek, J. N. H. *Chemistry* **2012**, *18*, 7091−7099.

(14) Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477−2480.

(15) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251−1259.

(16) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040−5042.

(17) Lumbroso, A.; Vautravers, N. R.; Breit, B. *Org. Lett.* **2010**, *12*, 5498−5501.

(18) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422−3434.

(19) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.

(20) Rodphaya, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiot.* **1986**, *39*, 629−635.

(21) Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, *1*, 13−17.

(22) Yang, H.; Kuroda, H.; Miyashita, M.; Irie, H. *Chem. Pharm. Bull.* **1992**, *40*, 1616−1618.

(23) Sabitha, G.; Chandrashekhar, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3824−3826.

(24) Hoegenauer, E. K.; Thomas, E. J. *Org. Biomol. Chem.* **2012**, *10*, 6995−7014.

(25) Leemhuis, F. M. C.; Lambertus, T.; Zwanenburg, B. *J. Org. Chem.* **1993**, *58*, 7170−7179.

(26) Takano, S.; Murakami, T.; Samizu, K.; Ogasawara, K. *Heterocycles* **1994**, *39*, 67−72.

(27) Kaisalo, L.; Koskimies, J.; Hase, T. *Synth. Commun.* **1999**, *29*, 399−407.

(28) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021−3024.

(29) Babu, K. V.; Sharma, G. V. M *Tetrahedron: Asymmetry* **2008**, *19*, 577−583.

(30) Bestmann, H. J.; Kellermann, W.; Pecher, B. *Synthesis* **1993**, *1*, 149−152.

(31) Hamada, T.; Daikai, K.; Irie, R.; Katsuki, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2441−2451.

(32) Yu, X.; Sun, D. *Molecules* **2013**, *18*, 6230−6268.

(33) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194−2207.

(34) Kis, Z.; Furger, P.; Sigg, H. P. *Experientia* **1969**, *25*, 123−124.

(35) Grove, J. F. *J. Chem. Soc., C* **1971**, *12*, 2261−2263.

(36) Ghisalberti, E. L.; Hargreaves, J. R.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2002**, *55*, 233−236.

(37) Chrysayi-Tokousbalides, M.; Machera, K.; Kyriakopoulou, K.; Aliferis, K. A.; Schrader, K. K.; Tsoutsanis, I.; Anastasiadou, P. *Bull. Environ. Contam. Toxicol.* **2007**, *79*, 499−503.

(38) Aliferis, K. A.; Chrysayi-Tokousbalides, M. *J. Agric. Food Chem.* **2006**, *54*, 1687−1692.

(39) Hirao, T.; Fujihara, Y.; Kurokawa, K.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1986**, *51*, 2830−2832.

(40) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1499−1502.

(41) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841−844.

(42) Amigoni, S.; LeFloch, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 2827−2831.

(43) Yadav, J. S.; Reddy, U. V. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 5984−5986.
(44) Oh, H.-S.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 2869−2870.
(45) Yadav, J.; Reddy, G.; Rao, T.; Reddy, B.; Khazim Al Ghamdi, A. *Synthesis* **2012**, *44*, 783−787.
(46) Nuguri, S.; Vuppula, N. K.; Eppakayala, L.; Rajasekhara, P. K. *J. Pharm. Res.* **2013**, 559−564.
(47) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247−7255.
(48) Doucet, H.; Derrien, N.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1998**, *551*, 151−157.
(49) Dimitriadis, C.; Gill, M.; Harte, M. F. *Tetrahedron: Asymmetry* **1997**, *8*, 2153−2158.
(50) Yadav, J. S.; Subba Reddy, B. V.; Rao, K. S.; Harikishan, K. *Synlett* **2002**, *2002*, 826−828.
(51) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860−2865.
(52) Grabley, S.; Hammann, P.; Huetter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176−1181.
(53) Göhrt, A.; Zeeck, A.; Hütter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 56−65.
(54) Mayer, M.; Thiericke, R. *J. Antibiot.* **1993**, *46*, 1372−1380.
(55) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 5739−5742.
(56) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381−6382.
(57) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett.* **1995**, *1*, 43−44.
(58) Solladié, G.; Arce, E.; Bauder, C.; Carreño, M. C. *J. Org. Chem.* **1998**, *63*, 2332−2337.
(59) Esumi, T.; Kimura, R.; Mori, M.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Heterocycles* **2000**, *52*, 525−528.
(60) Lukesh, J. M.; Donaldson, W. A. *Tetrahedron: Asymmetry* **2003**, *14*, 757−762.
(61) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73−78.
(62) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2006**, *47*, 1333−1335.
(63) Rawat, V.; Chouthaiwale, P. V.; Suryavanshi, G.; Sudalai, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2173−2177.
(64) Zúñiga, A.; Pérez, M.; Pazos, G.; Gómez, G.; Fall, Y. *Synthesis* **2010**, *2010*, 2446−2450.
(65) Martin, S. R.; Guinn, D. E. *Synthesis* **1991**, *1991*, 245−262.
(66) Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807−3810.
(67) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, *17*, 2651−2662.
(68) Hiscock, S. D.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **1998**, *54*, 11567−11580.
(69) Oppolzer, W.; Walther, E.; Balado, C. P.; Brabander, J. D. *Tetrahedron Lett.* **1997**, *38*, 809−812.
(70) Santelli-Rouvier, C.; Lefrère, S.; Santelli, M. *Tetrahedron Lett.* **1994**, *35*, 6101−6104.
(71) Ouvrard, N.; Rodriguez, J.; Santelli, M. *Tetrahedron Lett.* **1993**, *34*, 1149−1150.
(72) Hacini, S.; Santelli, M. *Tetrahedron* **1990**, *46*, 7787−7792.
(73) Miyashita, M.; Hoshino, M.; Yoshikoshi, A.; Kawamine, K.; Yoshihara, K.; Irie, H. *Chem. Lett.* **1992**, *6*, 1101−1104.
(74) Pilli, R. A.; de Andrade, C. K. Z. *J. Braz. Chem.* **1996**, *7*, 279−283.
(75) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005−6008.
(76) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574.
(77) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.
(78) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681−682.
(79) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit Bee, V.; Zhu, Y.; Burgess, K. *Chem.—Eur. J.* **2007**, *13*, 7162−7170.
(80) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett.* **2011**, *13*, 320−323.
(81) Otera, J.; Dan-oh, N.; Nozaki, H. *Tetrahedron* **1993**, *49*, 3065−3074.
(82) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588−5593.
(83) Claridge, T. D. W.; Davies, S. G.; Polywka, M. E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D. *Org. Lett.* **2008**, *10*, 5433−5436.
(84) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Chem. Commun.* **2005**, *15*, 1988−1989.
(85) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031−1035.
(86) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113−123.
(87) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208−5217.
(88) Morandi, S.; Pellati, F.; Benvenuti, S.; Prati, F. *Tetrahedron* **2008**, *64*, 6324−6328.
(89) Kermagoret, A.; Braunstein, P. *Organomet.* **2008**, *27*, 88−99.