

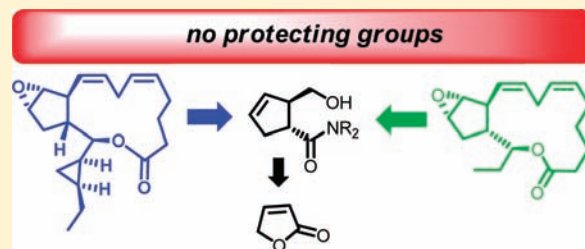
Catalysis-Based and Protecting-Group-Free Total Syntheses of the Marine Oxylipins Hybridalactone and the Ecklonialactones A, B, and C

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Supporting Information

ABSTRACT: Concise and protecting-group-free total syntheses of the marine oxylipins hybridalactone (**1**) and three members of the ecklonialactone family (**2–4**) were developed. They deliver these targets in optically pure form in 14 or 13 steps, respectively, in the longest linear sequence; five of these steps are metal-catalyzed and four others are metal-mediated. The route to either **1** or **2–4** diverges from the common building block **22**, which is accessible in 7 steps from 2[5H]furanone by recourse to a rhodium-catalyzed asymmetric 1,4-addition reaction controlled by the carvone-derived diene ligand **35** and a ring-closing alkene metathesis (RCM) catalyzed by the ruthenium indenylidene complex **17** as the key operations. Alternatively, **22** can be made in 10 steps from furfural via a diastereoselective three-component coupling process. The further elaboration of **22** into hybridalactone as the structurally most complex target with seven contiguous chiral centers was based upon a sequence of cyclopropanation followed by a vanadium-catalyzed epoxidation, both of which were directed by the same free hydroxy group at C15. The macrocyclic scaffold was annulated to the headgroup by means of a ring-closing alkyne metathesis reaction (RCAM). In response to the unusually high propensity of the oxirane of the targeted oxylipins for ring opening, this transformation had to be performed with complexes of the type $[(\text{Ar}_3\text{SiO})_4\text{Mo}\equiv\text{CPh}][\text{K}\cdot\text{OEt}_2]$ (**43**), which represent a new generation of exceedingly tolerant yet remarkably efficient catalysts. Their ancillary triarylsilanolate ligands temper the Lewis acidity of the molybdenum center but are not sufficiently nucleophilic to engage in the opening of the fragile epoxide ring. A final semireduction of the cycloalkyne formed in the RCAM step to the required (*Z*)-alkene completed the total synthesis of (–)-**1**. The fact that the route from the common fragment **22** to the ecklonialactones could follow a similar logic showcased the flexibility inherent to the chosen approach.



INTRODUCTION

Hybridalactone (**1**) was the first marine oxylipin to be isolated that contained a cyclopropane and a macrolactone moiety.¹ Derived from antimicrobial extracts of the red alga *Laurencia hybrida*, the constitution of this then very unusual secondary metabolite was established by the isolation team, and a partial assignment of its relative stereochemistry could be made on the basis of the recorded spectral data.¹ However, it was a captivating biosynthetic hypothesis, which allowed Corey and co-workers to anticipate the entire stereostructure as well as the absolute configuration of **1** (Scheme 1).²

According to this pathway, the hydroperoxide formed upon *S*-selective 12-lipoxygenation³ of eicosapentaenoic acid enters a cationic manifold, which engenders the selective formation of both carbocyclic rings and the macrolide backbone as shown in Scheme 1. This prediction was confirmed by the total synthesis of (–)-**1**⁴ as well as by a crystal structure analysis of a bromohydrin derived from an authentic sample.^{2,5} From the conceptual viewpoint, Corey's biosynthetic proposal innately linked the metabolic oxygenation pathways of polyunsaturated fatty acids with the intriguing chemistry of "nonclassical" carbocations of the homoallyl/cyclopropylmethyl type,⁶ which implied the occurrence of many more cyclopropyl-containing oxylipins in nature.

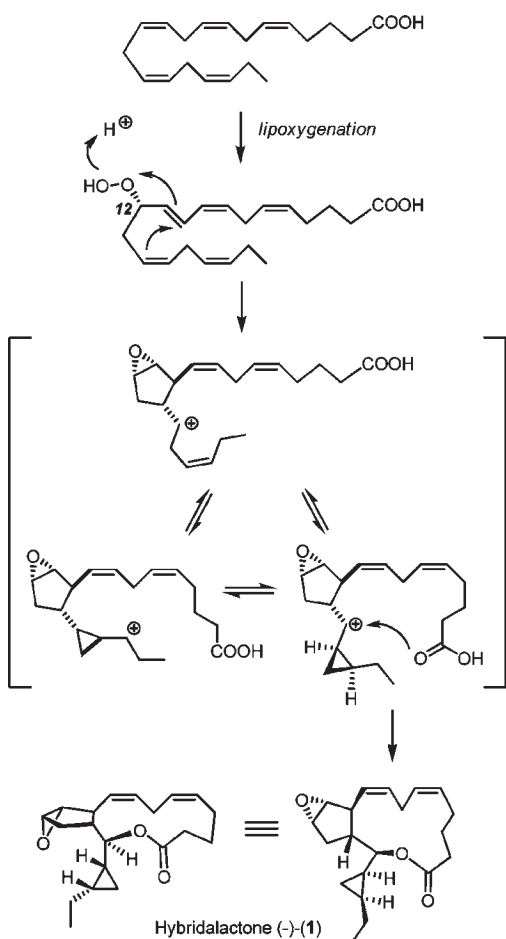
As is now well documented in the literature, this conjecture also turned out to be correct.^{7,8}

Various brown algae were later found to produce closely related oxylipins with C-18 carbon chains (rather than the C-20 skeleton of **1**).^{9–11} Although formally classified into three different series, the individual members of the ecklonialactone, eisenialhalide, and egregiachloride families likely derive from a common biosynthetic pathway; this path must closely follow the initial steps outlined above for hybridalactone but is less complex in that it lacks the "nonclassical cation" component (Scheme 2).¹² Whereas the ecklonialactones A (**2**) and B (**3**) originate from an intramolecular attack of the carboxylic acid terminus on the cation generated upon lipoxygenation of the fatty acid and subsequent cyclopentane formation, interception of the very same intermediate by external chloride leads to the egregiachlorides **8** and **9**.¹³ Ecklonialactones C (**4**) and D (**5**) as well as the eisenialhalides **6** and **7** derive from the parent compounds **2** and **3** by nucleophilic opening of the epoxide ring.^{9b,11} Another interesting variation is borne out in oxylipin **10** isolated from *Eisenia bicyclis*, in which reaction of the proximate double bond in **2** with

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Scheme 1. Proposed Biosynthetic Pathway Explaining the Constitution and Stereostructure of Hybridalactone (–)-1



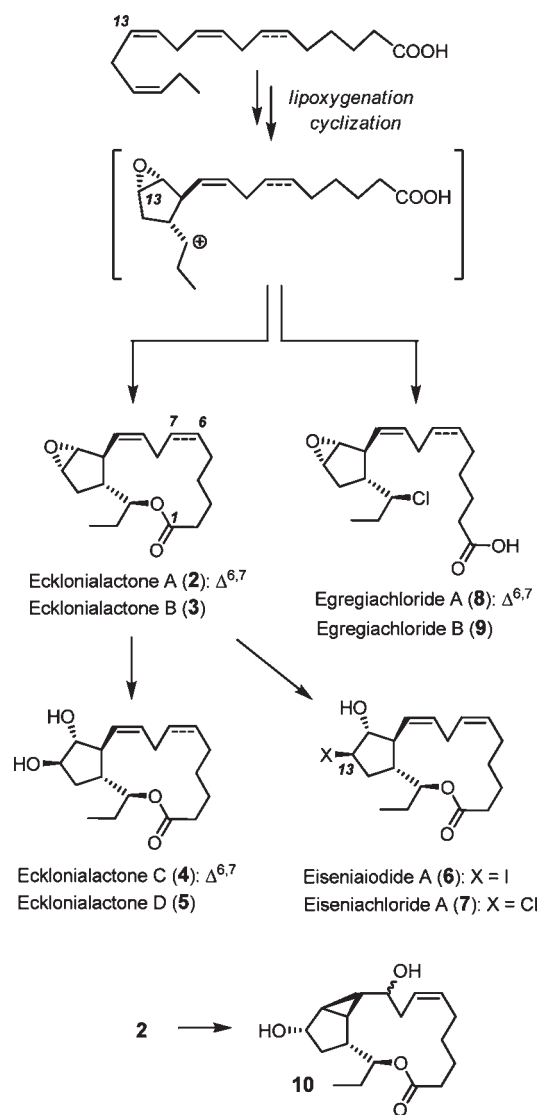
the labile epoxide ring gives rise to an annulated cyclopropane motif; the configuration of this particular compound at C9, however, has not yet been elucidated.¹¹

The fascinating structural diversity of these and related marine oxylipins originating from now well-understood biosynthetic machinery stands in marked contrast to the lack of information about their biological role in the producing organisms. It is generally assumed that they are part of the chemical defense mechanism of the algae against herbivores and/or microbial pathogens and could therefore be interesting lead structures of proven low cytotoxicity.^{9b,14} Yet, the limited supply of any of these marine lipids hampered more detailed assessments in the past. We now present a concise entry into hybridalactone and the ecklonialactone family via a common advanced precursor.^{15,16} The stunning chemoselectivity of contemporary homogeneous catalysis in general and the ability to rigorously distinguish between alkenes and alkynes in oxidative, reductive, as well as metathetic maneuvers in particular constitute the key enabling features. As a result, the final routes to these unusual lipids of marine origin are short, productive, enantioselective, and devoid of any protecting group manipulations.

RESULTS AND DISCUSSION

Strategic Considerations. Despite the many tremendous advances during the last decades,¹⁷ contemporary natural product

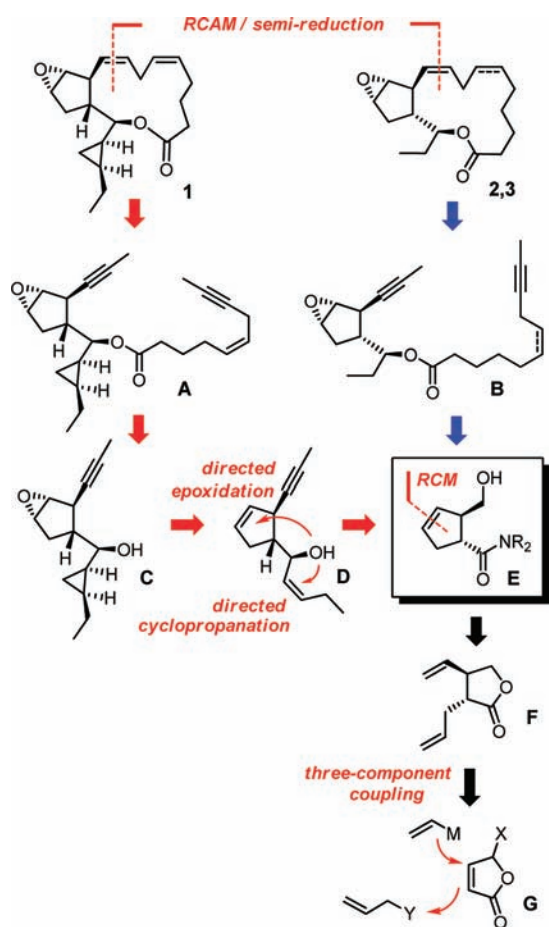
Scheme 2. Biosynthesis of the Ecklonialactones and Related Oxylipins with a C-18 Chain



total synthesis has to cope, more often than not, with protecting group chemistry as a necessary evil. Such manipulations are structurally unproductive and hence adversely affect all desirable “economies” of synthesis.¹⁸ The pursuit of increasingly complex targets in a protecting group-free format poses considerable practical and intellectual challenges yet constitutes an inspirational framework for chemical invention.¹⁹ A closer analysis of the published success stories, however, shows that a significant part of them deals with alkaloid or terpenoid targets, whereas polyketides and carbohydrates are rare, and even lipids are underrepresented.^{19–21}

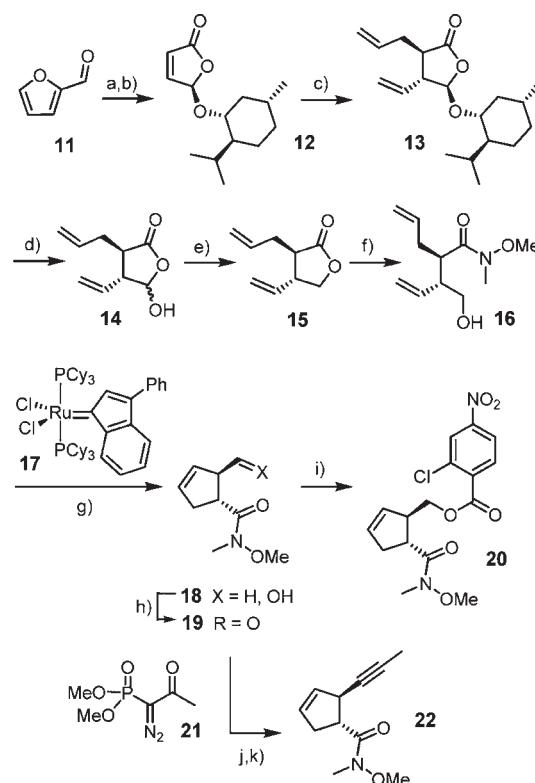
Following up on our previous investigations on prostanoids of marine origin,^{22,23} we were committed to developing a concise approach to hybridalactone under the premise of minimizing protecting group manipulations; in the ideal case, none would be required en route to this lipidic target containing seven contiguous chiral centers. At the same time, the chosen route should be flexible enough to allow for a late-stage bifurcation toward the ecklonialactone series as well.

Scheme 3. Retrosynthetic Analysis of Hybridalactone and the Ecklonialactones, Diverging at the Common Synthone E

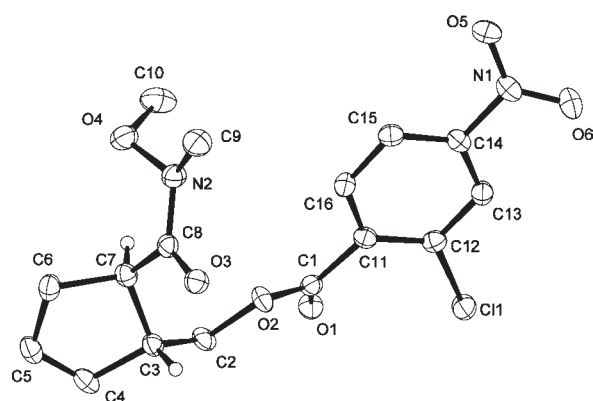


Our retrosynthetic analysis (Scheme 3) suggested that the proven orthogonal character of ring-closing alkene metathesis (RCM, $F \rightarrow E$)²⁴ and ring-closing alkyne metathesis (RCAM, $A \rightarrow 1$, $B \rightarrow 2,3$)^{25,26} could be favorably exploited for the assembly of the carbon skeleton,²⁷ whereas a properly configured C15-OH group in **D** might serve as a strategic relay to direct both the asymmetric cyclopropanation of a *cis*-configured allylic double bond and the epoxidation of the more distant olefinic site within the five-membered headgroup. Fragment **D** was envisaged to derive from **E**; this building block would also serve as the cornerstone en route to the Ecklonialactones, which have a shorter carbon chain but a larger, 14-membered lactone ring. Further analysis then leads back via **F** to commercial 2[5*H*]-furanone (**G**, $X = H$) or derivatives thereof ($X \neq H$), which ideally might be functionalized with the required olefinic appendices in a one-pot, three-component coupling process.^{28,29}

Original Auxiliary-Based Route to the Headgroups. In an initial foray, recourse was made to the proven versatility of *L*-(-)-menthol as a chiral auxiliary³⁰ since butenolide **12** is known to participate well in conjugate addition reactions of various nucleophiles including organocopper reagents (Scheme 4).³¹ Moreover, **12** is available from cheap furfural (**11**) in two high-yielding operations without need for a chromatographic purification.^{32,33} Addition of the copper reagent derived from vinylmagnesium bromide and CuI to a solution of **12** in THF

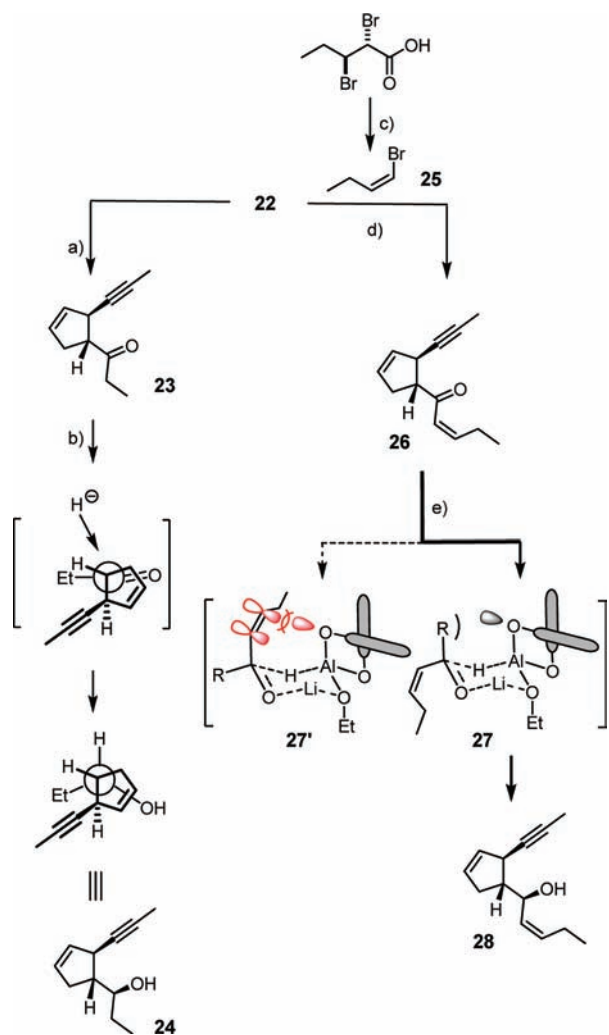
Scheme 4^a

^a Reagents and conditions: a) O_2 , rose Bengal, $h\nu$, MeOH, 79%; b) *L*-menthol, CSA cat., toluene, reflux, then recrystallization from hexanes, cf. ref 33; c) $H_2C=CHMgBr$, CuI, THF, $-78^\circ C$, then allyl iodide, $-60^\circ C$, 2 h, 86%; d) aq. TFA, 16 h, 95%; e) $NaBH_4$, MeOH, 2 h, then HCl in Et_2O , reflux, 1 h, 75%; f) $Me(MeO)NH \cdot HCl$, Me_3Al , CH_2Cl_2 , 4 h; g) **17** (4 mol %), CH_2Cl_2 , 16 h, 74% (over both steps); h) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2 , 1.5 h, 73%; i) 2-chloro-4-nitrobenzoyl chloride, Et_3N , DMAP cat., CH_2Cl_2 , 16 h, 65%; j) **21**, K_2CO_3 , MeOH, 16 h, 75%; k) LiHMDS, $MeOTf$, THF, $-78^\circ C$, 2.5 h, 80%.

Figure 1. Structure of compound **20** in the solid state.³⁴

followed by an allyl iodide quench furnished the desired three-component adduct **13** in 86% yield as a single diastereomer on a multigram scale. Acid-catalyzed cleavage of the auxiliary and subsequent reduction of the resulting hemiacetal **14** with $NaBH_4$ gave butenolide **15** in excellent overall yield.

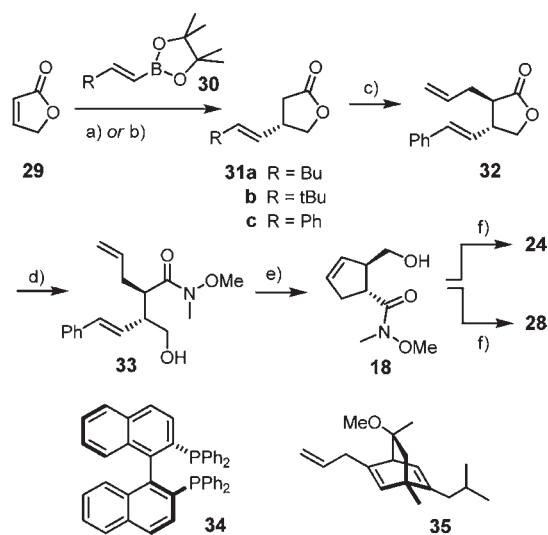
This product was then ring opened to the corresponding Weinreb amide **16**,³⁵ which was found to revert to lactone **15**

Scheme 5^a

^a Reagents and conditions: a) EtMgBr, THF, 0 °C, 30 min, 93%; b) LiBH(*sec*-Bu)₃, THF, -78 °C, 2 h, 69%; c) NaHCO₃, DMF, 70 °C, 130 mbar, 1 h, 87%; d) (i) **25**, Li sand, Et₂O, 80 min, -50 °C; (ii) **22**, THF, 0 °C, 1 h, 83%; e) LiAlH₄, (*R*)-BINOL, EtOH, THF, -78 °C, 72 h, 90% (dr >10:1), see text.

fairly quickly. Therefore, this diene was immediately subjected to ring-closing olefin metathesis using the ruthenium indenylidene complex **17** previously described by our group as a cost-effective alternative to the classical Grubbs catalyst.^{36–39} Cyclopentene **18** was thus obtained in a well-reproducible yield of 74% over both steps. To confirm the integrity of this key intermediate, **18** was transformed into the crystalline ester derivative **20**. Not only did the structure of **20** in the solid state show the *trans* disposition of the lateral chains, but the chloride substituent also facilitated the determination of the absolute configuration of this product (Figure 1). As expected, the elaboration of **18** into enyne **22** as the key building block of the projected syntheses by oxidation with Dess–Martin periodinane,⁴⁰ Ohira–Bestmann reaction,⁴¹ and end-capping of the resulting terminal alkyne with a methyl group was straightforward and high yielding.

The syntheses of the ecklonialactones on the one hand and hybridalactone on the other hand diverge at this point (Scheme 5). Entry into the former series was gained upon reaction of **22** with EtMgBr to give ketone **23**, which was reduced

Scheme 6^a

^a Reagents and conditions: a) [Rh(cod)(MeCN)][BF₄] (1.5 mol %), (*S*)-BINAP (1.6 mol %), THF, H₂O, 65 °C, **31a** (65%, 82% ee), **31b** (17%, 86% ee), **31c** (64%, 73% ee), see Text; b) [Rh(C₂H₄)₂Cl]₂ (1.5 mol %), **35** (3.3 mol %), 1,4-dioxane, aq. KOH, 72 h, **31c** (52%, 80% ee, 93% ee after recryst.); c) LDA, THF, -78 °C, then allyl iodide, 80 min, 87%; d) HN(OMe)Me·HCl, Me₃Al, CH₂Cl₂, 2 h, 0 °C; e) **17** (8 mol %), CH₂Cl₂, 16 h, 75% (over both steps); f) see Schemes 4 and 5.

with *L*-selectride at -78 °C to deliver the required alcohol segment **24** as a single isomer. The stereochemical outcome is in line with a prototype Felkin–Ahn transition state and was confirmed by Mosher ester analysis at a later stage of the synthesis after epoxidation of the double bond.³⁴

The formation of the analogous allylic alcohol **28** required for the synthesis of hybridalactone turned out to be more delicate. Gram quantities of the necessary alkenyl bromide **25** were conveniently obtained in isomerically pure form (*Z*:*E* ≥ 96:4) by a base-promoted decarboxylative elimination of 2,3-dibromopentanoic acid, which itself is available on large scale by addition of Br₂ to 2*E*-pentenoic acid in CH₂Cl₂.⁴² However, the Grignard reagent derived from **25** reacted with Weinreb amide **22** to give the desired enone **26** only in 56% yield together with appreciable amounts of the more stable *E*-isomer (19%). Although these compounds could be separated by careful flash chromatography, product **26** isomerizes fairly quickly, thus rendering any lengthy purification protocol counterproductive. Gratifyingly, though, the lithium reagent formed on exposure of **25** to Li sand in Et₂O at low temperature led to a more favorable outcome, furnishing **26** in 83% yield with only minute amounts of the corresponding *E*-isomer being detectable.

Enone **26** thus formed was immediately subjected to 1,2-reduction to avoid any scrambling of the conjugated alkene. The use of *L*-selectride, which had been highly appropriate in the case of the analogous ethyl ketone **23**, gave the desired alcohol **28** as a single isomer but in a disappointing yield of only 31%. It required an extensive screening of chiral and achiral reducing agents until a satisfactory solution could be found.³⁴ The best results were obtained with a combination of LiAlH₄, (*R*)-BINOL (1 equiv), and EtOH (1 equiv) in THF at -78 °C.⁴³ Under these conditions, the desired allylic alcohol **28** was obtained in 90% yield with a diastereomeric ratio of >10:1.⁴⁴ The outcome is consistent with a transition state model,⁴³ in which the

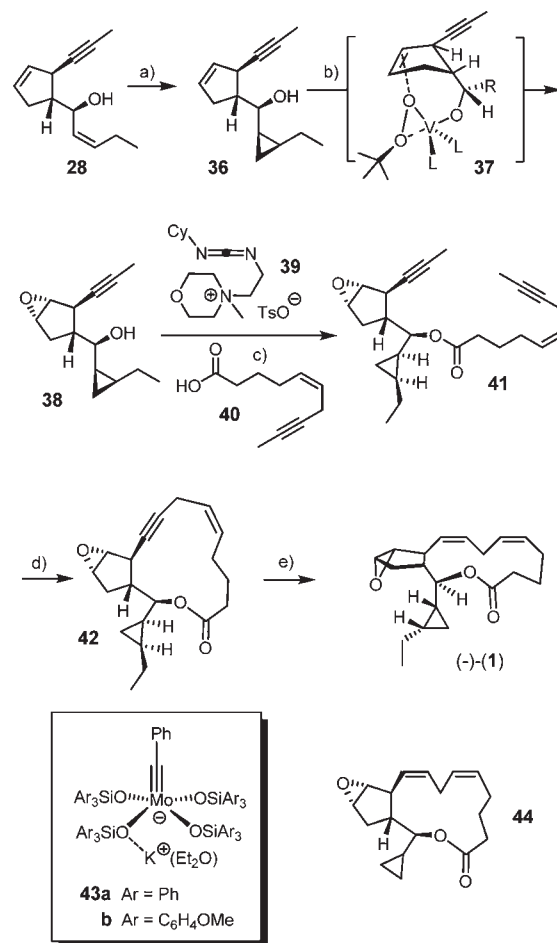
n/π -repulsion between the conjugated double bond of enone **26** and the oxygen lone pair of the axially disposed binaphtholate oxygen atom in **27'** is much more destabilizing than the steric effects between this oxygen and the axially oriented group R in the diastereomeric array **27**.

Auxiliary-Free and Catalysis-Based Approach. Although the route described above was highly productive and could be conveniently performed on a large scale and—strictly speaking—the use of an auxiliary does not fall into the category of protecting group chemistry, an attempt was made to find an even more direct entry into the headgroups of the targeted oxylipins. To this end, the asymmetric 1,4-addition of alkenylboronic acid derivatives to 2[*SH*]-furanone in the presence of a chiral rhodium catalyst was considered, even though successful applications of this methodology to α,β -unsaturated esters or lactones are still scarce.^{45,46}

To ensure crystallinity of the downstream products as well as for convenience of preparation and handling, various substituted alkenylboronates **30** ($R \neq H$) were tested and found to add to butenolide **29** in moderate to good yields in the presence of a catalyst formed in situ from $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$ and (*S*)-BINAP (**34**) in aqueous THF at $\geq 60^\circ\text{C}$ (Scheme 6). Even though the desired 1,4-adducts **31** were obtained with an encouraging ee of up to 86%, the fairly harsh conditions led to partial migration of the alkene into conjugation with the lactone carbonyl. Gratifyingly though, the use of the carvone-derived diene ligand **35** instead of BINAP allowed the rhodium-catalyzed conjugate addition to be carried out at ambient temperature without isomerization interfering.⁴⁶ As the resulting adduct **31c** derived from styrenylboronate **30c** ($R = \text{Ph}$) turned out to be nicely crystalline, the optical purity of the compound could be increased from 80% ee to a workable 93% ee by a single recrystallization.

GC analysis on a chiral stationary phase proved that the use of either (*S*)-BINAP (**34**) or the (–)-carvone-derived diene **35** furnished the same enantiomer of **31c**; its configuration was assigned according to the transition state models proposed in the literature⁴⁷ and confirmed by comparison with literature data.⁴⁸ Moreover, its identity with the material obtained via the auxiliary-based route described above, the configuration of which had been proven by X-ray diffraction, was firmly established after α -allylation. This step was accomplished by deprotonation of **31c** with LDA and trapping of the resulting enolate with allyl iodide. The subsequent opening of lactone **32** to the corresponding Weinreb amide **33** followed by RCM furnished cyclopentene **18**, which was identical to the material described above in all regards. It is of note that the metathetic ring closures of the styryl derivative **33** and the vinyl derivative **16** (see Scheme 4) with the aid of the ruthenium indenylidene complex **17**³⁶ are equally productive. Compound **18** thus obtained intercepts the previous route and could be elaborated into the key building blocks **24** and **28** as outlined above.

Whereas the auxiliary-based approach is inherently longer, it enjoys the practical convenience of being readily scalable and features the beauty of a concise three-component coupling event, which is not yet possible in the rhodium-catalyzed sequence. The latter, however, is distinguished by its directness, avoiding any steps that do not contribute straight to the build-up of the carbon framework of the target molecule. In any case, the effectiveness of either route to the common intermediate **18** secured a good material supply and therefore formed a sound basis for the completion of the projected total syntheses.

Scheme 7^a

^a Reagents and conditions: a) CH_2I_2 (4 equiv), Et_2Zn (2 equiv), CH_2Cl_2 , -20°C , 16 h, 65%; b) *t*BuOOH, $\text{VO}(\text{acac})_2$ (15 mol %), MS 3 Å, CH_2Cl_2 , 5 h, 69%; c) **39**, acid **40**, DMAP cat., CH_2Cl_2 , 7 d, 77%; d) **43b** (15 mol %), MS 5 Å, toluene, 70°C , 24 h, 79%; e) P2-Ni (cat.) [prepared from $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, NaBH_4 , ethylenediamine], H_2 (1 atm), EtOH, 3 h, 84%.

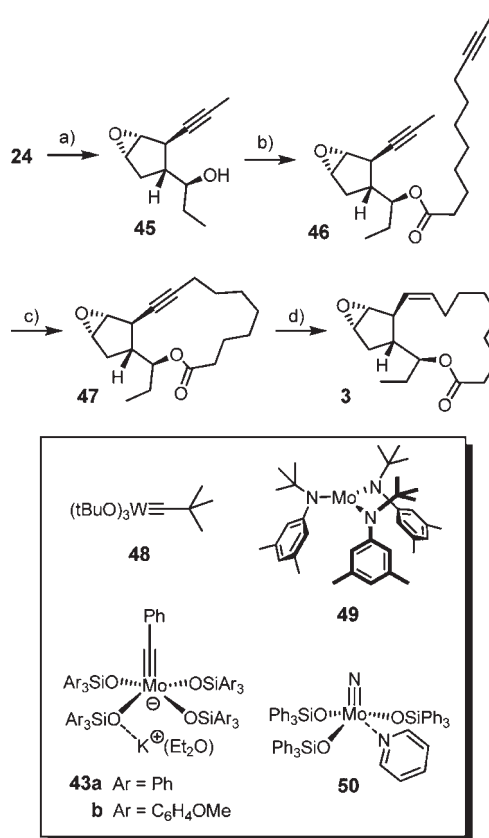
Total Synthesis of Hybridalactone. With compound **28** in hand, the project entered the critical phase of diastereoselective formation of both sensitive three-membered ring motifs decorating the backbone of hybridalactone with the aid of the 15-OH group as a key relay substituent.⁴⁹ To this end, the *Z*-configured allylic alcohol **28** was engaged in a *syn*-selective cyclopropanation on reaction with the zinc carbenoid generated in situ from CH_2I_2 and Et_2Zn (Scheme 7). However, the very fragile nature of our substrate and the presence of a second double bond as well as of an alkyne, both of which must survive unchanged, precluded direct application of the conditions described in the literature.⁵⁰ In particular, the use of a prescribed 1:1 ratio between CH_2I_2 and Et_2Zn and of a fairly large excess of the active component at 0°C led to extensive degradation. After some experimentation, it was found that the combination of 4 equiv of CH_2I_2 with only 2 equiv of Et_2Zn in CH_2Cl_2 gave the desired cyclopropane **36** in well reproducible 65% yield as a single isomer, provided that the reaction was carried out at -20°C . Likewise, the subsequent hydroxyl-directed epoxidation of the remaining olefinic site in **36** with a combination of *t*BuOOH and catalytic $\text{VO}(\text{acac})_2$ turned

out to be exquisitely selective,⁵¹ delivering the rather labile product **38**, in which all seven contiguous chiral centers of hybridalactone are appropriately set. Assuming the usual trigonal bipyramidal coordination geometry for the loaded vanadium complex and a backside displacement of the O–O bond⁵¹ allows a reasonable transition state model **37** to be formulated, which nicely accounts for the observed outcome. The analysis of the derived Mosher esters confirmed the stereochemistry assigned to this key intermediate.^{34,52}

Not unexpectedly, the esterification of **38** with acid **40**⁵³ was rather challenging. The proclivity of the epoxide ring of such oxylipins to undergo ring opening had been anticipated from the host of known natural products formed upon nucleophilic attack of water or halide onto the oxirane of the parent Ecklonialactones (see Scheme 2). This pronounced bias pertains to **38** and related building blocks (see below) and precluded the use of all esterification methods that contain or produce any nucleophilic species in the reaction mixture (acid chloride, acid fluoride, mixed anhydrides, *N*-methyl 2-chloropyridinium chloride, etc). Moreover, Lewis-acid-catalyzed transesterification methods are not applicable as they destroy the very sensitive cyclopropylcarbinol motif.⁵⁴ Further complications arose from the fact that the dicyclohexylurea derived from DCC proved to be inseparable by flash chromatography from the desired ester **41**. Gratifyingly, however, it was found that the modified carbodiimide **39** escorted by an only weakly nucleophilic tosylate anion furnished product **41** in respectable 77% yield.⁵⁵

Exposure of this compound to catalytic amounts of the molybdenum alkylidyne complex **43a** as the prototype member of the latest generation of alkyne metathesis catalysts effected gentle closure of the macrocyclic scaffold (Scheme 7).⁵⁶ However, the resulting product **42** and the triphenylsilanol released from the catalyst upon workup were difficult to separate by conventional means. This problem could be fixed by using complex **43b** bearing *p*-methoxyphenyl groups on the silanolate ligands, which could be easily removed by standard flash chromatography; the activity of the catalyst remains largely unchanged by this peripheral modification.⁵⁷ Although the strain of the emerging 13-membered cycle containing a stiff 1,4-enyne moiety mandated a reaction temperature of 70 °C and application of high dilution conditions (0.002 M), the desired product **42** was obtained in well reproducible 79% yield. As previously described by our group, the silanolate ligand sphere of the molybdenum alkylidyne catalyst is key to success:⁵⁶ it imposes a well-balanced level of Lewis acidity onto the Mo(+6) center, which is high enough to ensure excellent reactivity in alkyne metathesis yet sufficiently tempered to guarantee outstanding compatibility with a host of polar substituents; the current example extends this list to the fragile cyclopropylcarbinol ester, oxirane, and skipped enyne moieties featured in **42**. Moreover, the silanolates themselves do not engage in nucleophilic opening of the unusually reactive epoxide rings of the substrate and/or the resulting product even at elevated temperatures. The rigorous distinction of the catalyst between the alkynes and the pre-existing *Z*-alkene in **42** was also imperative for the present application. The superior performance of complexes **43** will become even more obvious by the comparative investigation conducted in the Ecklonialactone series (see below).

Final semihydrogenation of cycloalkyne **42** with the aid of colloidal P2-nickel⁵⁸ in the presence of ethylenediamine gave hybridalactone (–)-**1** in 84% yield with <5% overreduction. The analytical and spectral data of the final product were in excellent

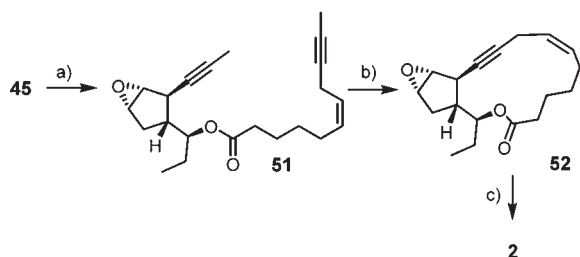
Scheme 8^a

^a Reagents and conditions: a) VO(acac)₂ (8 mol %), *t*BuOOH, CH₂Cl₂, 3 h, 94%; b) 9-undecynoic acid, **39**, DMAP cat., CH₂Cl₂, 16 h, 61%; c) **43a** (4 mol %), toluene, MS 5 Å, 3 h, 80%, or: **43b** (4 mol %), toluene, MS 5 Å, 3 h, 94%; d) Lindlar catalyst, H₂ (1 atm), CH₂Cl₂, 2.5 h, 90%.

agreement with those of the natural product reported in the literature.¹ Overall, (–)-**1** was obtained in 14 (Rh-catalyzed route) or 17 steps (auxiliary-based route) over the longest linear sequences, respectively, without any protecting group chemistry whatsoever in either route. Except for the final Lindlar-type reduction of the cyclic alkyne, the sequence also adheres to the logic of a linearly escalating oxidation state management set forth in the recent literature.⁵⁹

As an initial foray into the preparation of analogues, we targeted desethyl-hybridalactone (**44**) differing from (–)-**1** only in the absence of the lateral ethyl substituent on the cyclopropyl unit. Whereas this formal deletion is thought to be a minor change in functional regard, it greatly simplifies the synthesis by avoiding the delicate stereoselective cyclopropanation. The synthesis of **44** is outlined in detail in the Supporting Information.

Ecklonialactone A, B and C. Along similar lines, the total syntheses of the C18 oxylipins Ecklonialactone A and B could be readily completed.^{15,60} Starting from building block **24**, a hydroxyl-directed vanadium-catalyzed epoxidation gave **45**, the configuration of the secondary alcohol of which was confirmed by analysis of the derived Mosher esters.³⁴ As in the previous cases, it was necessary to effect the esterification of this alcohol with 9-undecynoic acid under the aegis of carbodiimide **39** since all other methods investigated led to side reactions of the epoxide ring or even complete destruction of this valuable material (Scheme 8).⁶¹

Scheme 9^a

^a Reagents and conditions: a) undec-6Z-en-9-ynoic acid, **39**, DMAP cat., CH₂Cl₂, 16 h, 65%; b) **43b** (5 mol %), MS 5 Å, toluene, 7 h, 90%; c) P2-Ni (25 mol %), H₂ (1 atm), EtOH, 2 h, 69%.

With good amounts of diyne **46** in hand, a comparative investigation was carried out, which showcased the superiority of complexes of type **43** in the subsequent ring-closing alkyne metathesis reaction. As anticipated, **43a** and **43b** both furnished the desired cycloalkyne **47** in yields of 80% and 94%, respectively; once again, complex **43b** had the practical advantage of easier separation of the product from the silanolate ligands released from the catalyst during work up. In contrast to the hybridalactone series, however, the ring closure occurred smoothly even at ambient temperature in 0.02 M toluene solution. The lower ring strain of the 14-membered macrolactone **47** as compared to the 13-membered ring of **42** is thought to account for the milder conditions and the higher applicable concentration.

More significant is the observation that the classical tungsten Schrock alkylidyne complex (*t*BuO)₃W≡CCMe₃ (**48**), which serves as the benchmark in alkyne metathesis chemistry ever since its discovery,⁶² afforded none of the desired product due to instantaneous decomposition of the starting material. We tentatively ascribe this failure to the pronounced Lewis acidity of the high valent tungsten center in this complex. Likewise, the performance of [(*t*Bu)ArN]₃Mo (**49**, Ar = 3,5-dimethylphenyl), after in situ activation with CH₂Cl₂ as previously described,⁶³ was unsatisfactory. Unusually high loadings (20–40 mol %) of the precatalyst were necessary, and the yields of **47** obtained in different runs were variable (50–89%). Although this system had previously been found compatible with oxiranes,⁶⁴ GC/MS data indicated that the amide ligands present in [(*t*Bu)ArN]₃Mo partly reacted with substrate **46**, most likely by opening of its unusually sensitive epoxide ring. Likewise, precatalyst **50** cannot be applied because the nitrido function is known to react with oxiranes.^{65,66} Collectively, these results showcase the superior application profile of the readily available molybdenum alkylidynes of type **43** endowed with triarylsilanolate ligands, which are the most effective and, at the same time, most tolerant alkyne metathesis catalysts currently available.⁵⁶ Since these species need not be handled per se but can be conveniently released in situ from the corresponding phenanthroline adduct precursors, which for their part are fully air stable and can be stored and handled without any precautions,⁵⁶ alkylidynes of type **43** are also practical to use and hence deserve further consideration in the realm of advanced organic synthesis.⁶⁷

Diyne **51** containing an extra double bond was prepared analogously from the same starting material **45** and found to cyclize equally well on treatment with catalytic amounts of **43b** (Scheme 9). Cycloalkynes **52** and **47** were then transformed into

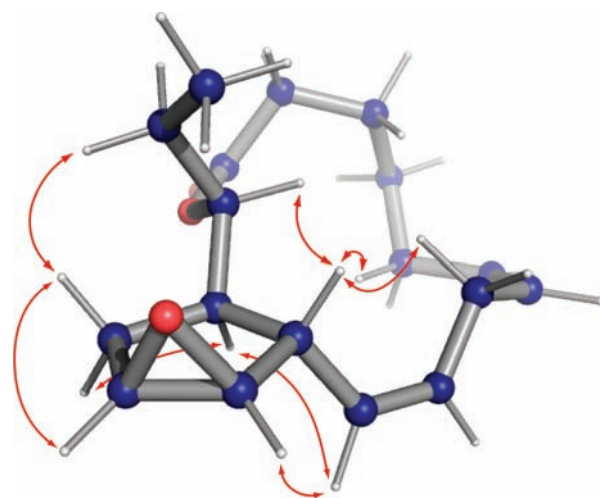
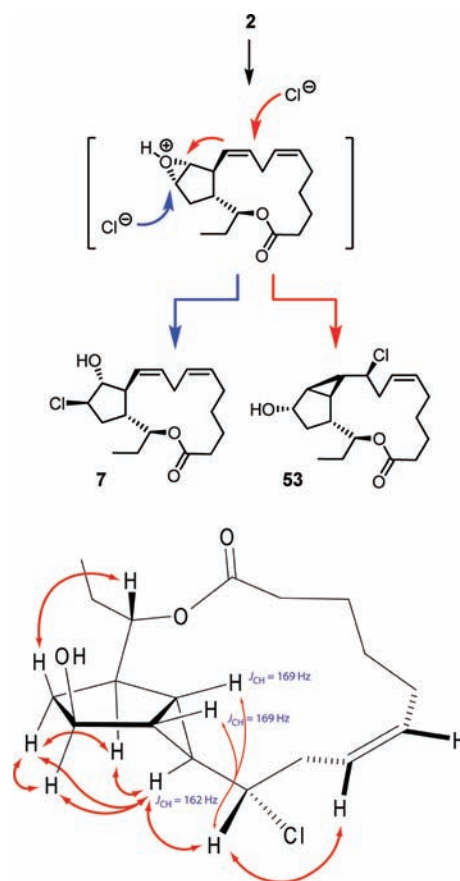


Figure 2. Geometry-optimized structure of ecklonialactone A (**2**), which is in excellent agreement with the experimentally observed NOE's (indicated as red arrows).

Scheme 10. Two Different Acid-Promoted Oxirane Opening Reactions of Ecklonialactone A and Stereostructure of the Derived Product 53 (Indicative NOE's Are Shown As Red Arrows)



ecklonialactone A (**2**) and B (**3**), respectively, by semireduction. Lindlar hydrogenation was effective in the latter case, whereas **52** required the use of P2-nickel⁵⁸ to avoid substantial over-reduction.

The recorded data of our samples matched those of the natural products.^{9–11} Since **2** is known to undergo clean opening of the epoxide ring on treatment with aqueous HClO₄ to give ecklonialactone C (**4**),¹⁰ a formal synthesis of this congener has also been accomplished.

Follow-Up Chemistry of Ecklonialactone A. Careful NMR spectroscopic investigations of our samples of ecklonialactone A (**2**) revealed strong transannular interactions across the macrocycle between the protons at the ring junction, in particular H11, and the methylene groups at C4 and C5 on the back side of the ring. These tight contacts are in good agreement with the compact geometry-optimized structure of **2** calculated with the OM3 semiempirical method (Figure 2).⁶⁸

When a sample of **2** was kept in CDCl₃, which had not been dried and distilled immediately prior to use, a fairly rapid and clean epoxide opening was observed, the outcome of which could be deduced from the characteristic spectral fingerprints of the resulting products (Scheme 10). Specifically, direct attack of chloride at the oxirane furnished the corresponding chlorohydrine, the data of which matched those of eiseniachloride A (**7**) in every regard.¹¹ Moreover, the formation of a second product derived from a more involved epoxide opening process was detected, to which we confidently ascribe structure **53**; whereas the constitution of this compound is definite, the stereochemistry of the chiral center at C9 bearing the chloride substituent could not be unambiguously determined, even though the observed NOE's strongly suggest the depicted configuration. This product originates from attack of the C9–C10 double bond onto the adjacent epoxide ring, which is favored by the close spatial proximity of these groups evident from Figure 2. Except for the chloride residue, product **53** corresponds to the unnamed oxylipin **10**, which was coextracted with ecklonialactone A (**2**) from the brown alga *Eisenia bicyclis*.¹¹

CONCLUSIONS

The use of protecting groups implicitly acknowledges an inability to solve (chemo)selectivity issues in a more direct manner. Although there is no reason to believe that the need to do so in the realm of natural product synthesis will cease anywhere close, an increasing number of case studies in the recent literature highlight the fact that this exigent goal can ultimately be reached.¹⁹ The work described in this paper adds some decently complex lipidic targets to this growing list. The challenges posed by the ecklonialactones and hybridalactone, which contain up to seven contiguous chiral centers and display quite reactive functional groups, were met by a sequence of metal-catalyzed and metal-mediated reactions, which exhibits respectable levels of atom-, redox-, and step-economy. Conceptually speaking, it is the ability to rigorously distinguish between the π -systems of alkenes and alkynes in reductive, oxidative, and metathetic transformations which formed the basis of the successful route and therefore represents an essential lesson to be learnt from this venture.

ASSOCIATED CONTENT

Supporting Information. Experimental Section, preparation of desethyl-hybridalactone, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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