

Protecting-Group-Free and Catalysis-Based Total Synthesis of the Ecklonialactones

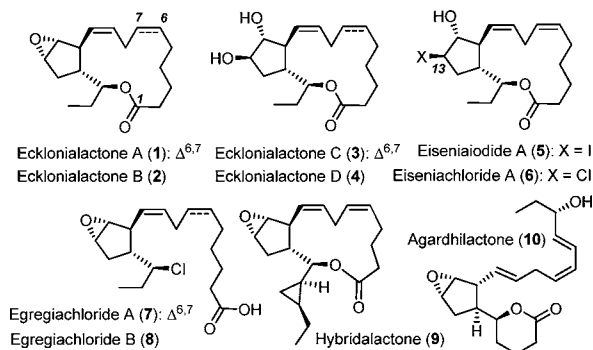
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Abstract: A concise and protecting-group-free total synthesis of optically pure ecklonialactones A (**1**) and B (**2**) is described. The successful route to these oxylipins isolated from various brown algae involves five transition-metal-catalyzed transformations in the longest linear sequence of 13 steps. The first chiral center was set by a rhodium-catalyzed 1,4-addition of an alkenyl boronate to the commercial butenolide **11**, which was controlled by Carreira's carvone-derived diene ligand **21**. Other key steps involve a ring-closing olefin metathesis effected by the ruthenium indenylidene complex **22** for the formation of the five-membered carbocycle, a vanadium-catalyzed, hydroxy-directed epoxidation, and a ring-closing alkyne metathesis (RCAM) to forge the macrocyclic ring. Because of the unusually high propensity of the oxirane of the ecklonialactones for ring-opening, this transformation was best achieved with $[(\text{Ph}_3\text{SiO})_3\text{Mo}\equiv\text{CPh}]\cdot\text{OEt}_2$ (**34**) as the catalyst, which is a representative of a new generation of highly tolerant yet remarkably efficient molybdenum alkylidyne complexes. The ancillary triphenylsilylanolate ligands in **34** temper the Lewis acidity of the molybdenum center and are not able to nucleophilically open the fragile epoxide ring. The final reduction of the cycloalkyne formed in the RCAM step to the required (*Z*)-alkene was accomplished either by Lindlar reduction or with the aid of nickel boride.

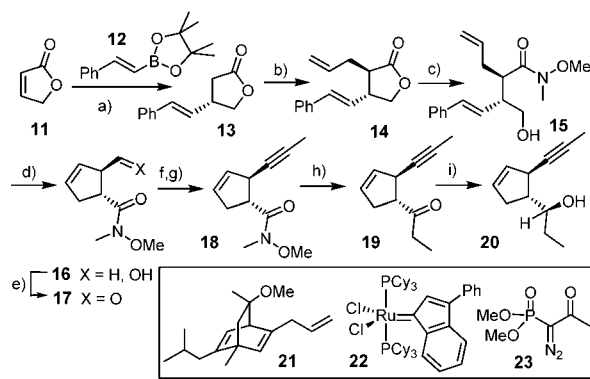
Despite tremendous strategic and methodological advances,¹ the art and science of natural product total synthesis is still far from mature. Even target molecules of moderate size usually impose significant protecting group requirements on a workable synthesis plan. As structurally unproductive steps, however, such manipulations adversely affect all desirable "economies" of synthesis.² The pursuit of complex targets without recourse to protecting group maneuvers was therefore recognized as a challenging yet inspirational frame for chemical invention.³



Among the limited number of protecting-group-free total syntheses documented in the literature, alkaloid targets are prominently

featured, whereas carbohydrates, polyketides, and fatty acids are currently under-represented.³ We now report a case study in the latter arena, in which metal-catalyzed reactions play a prominent role. Specifically, ecklonialactones A (**1**) and B (**2**) were chosen as the targets, which are the parent members of a family of C-18 oxylipins isolated from various brown algae.⁴ Opening of their epoxide ring delivers the ecklonialactones C (**3**) and D (**4**) or eiseniahalides (**5**, **6**) respectively, whereas the egriachlorides (**7**, **8**) derive from an assisted cleavage of the macrolactone.⁴ Furthermore, **1** and **2** are closely related to hybridalactone (**9**)⁵ and agardhilactone (**10**),⁶ two unusual eicosanoids from red algae. Although these oxylipins may be involved in the chemical defense of the producing organisms against herbivores, no in-depth assessment of their physiological properties has been published.⁷

Scheme 1^a

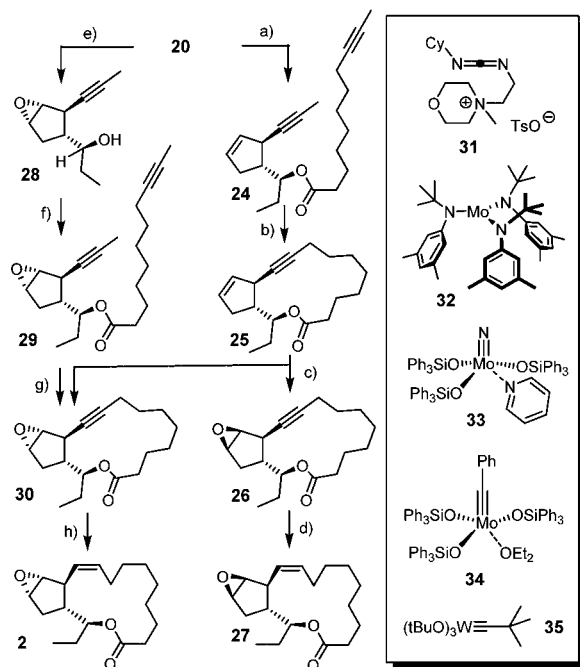


^a Reagents and conditions: (a) $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (1.5 mol %), **21** (3.3 mol %), SiO_2 cat., 1,4-dioxane, aq. KOH, 52%, 80% ee (93% ee after recryst.); (b) LDA, THF, -78°C , then allyl iodide, 87%; (c) $\text{HN}(\text{OMe})\text{Me}\cdot\text{HCl}$, Me_3Al , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt}$; (d) **22** (8 mol %), CH_2Cl_2 , 75% (over both steps); (e) Dess–Martin periodinane, NaHCO_3 , CH_2Cl_2 , 73%; (f) **23**, K_2CO_3 , MeOH, 75%; (g) LiHMDS, MeOTf, THF, -78°C , 80%; (h) EtMgBr , THF, 0°C , 93%; (i) $\text{LiBH}(s\text{-Bu})_3$, THF, -78°C , 69%.

Following up on our previous investigations on prostanoids of marine origin,⁸ we were committed to developing a concise entry into the ecklonialactone series.⁹ Commercial butenolide **11** served as the point of departure, undergoing a rhodium-catalyzed 1,4-addition of alkenylboronate **12** (Scheme 1).¹⁰ Although the reaction was only moderately selective (80% ee) when controlled by the (–)-carvone-derived diene ligand **21**,¹¹ the optical purity of **13** could be increased by recrystallization to a workable ee of 93%.¹² Deprotonation with lithium hexamethyldisilazide (LDA) followed by an allyl iodide quench then gave the *trans*-disubstituted lactone **14** in good yield. Its subsequent opening with $\text{HN}(\text{OMe})\text{Me}/\text{Me}_3\text{Al}$ proceeded well, but the resulting Weinreb amide **15** readily reverted to the starting lactone; therefore, the product was exposed without delay to the ruthenium indenylidene complex **22**, previously described by our group as a cost-effective alternative to the classical

Grubbs catalyst.¹³ The ensuing ring-closing metathesis provided cyclopentene **16** in 75% yield over two steps, which was elaborated into enyne **18** by oxidation, Ohira–Bestmann reaction,¹⁴ and end-capping of the resulting alkyne with a methyl group. Reaction of **18** with EtMgBr gave ketone **19**, which was reduced with L-Selectride to deliver the required alcohol segment **20**.

Scheme 2^a



^a Reagents and conditions: (a) 9-undecynoyl chloride, DMAP, CH₂Cl₂, 70%; (b) **32** (20 mol %), toluene/CH₂Cl₂, 80 °C, 71%; (c) dimethyl dioxirane, acetone/CH₂Cl₂, -78 °C → rt, 75% (**26:30** = 3:1); (d) Lindlar catalyst, H₂, CH₂Cl₂, 80%; (e) VO(acac)₂ (8 mol %), *t*-BuOOH, CH₂Cl₂, 94%; (f) 9-undecynoic acid, **31**, DMAP, CH₂Cl₂, 61%; (g) **34** (5 mol %), toluene, MS 5 Å, 80%; (h) Lindlar catalyst, H₂, CH₂Cl₂, 90%.

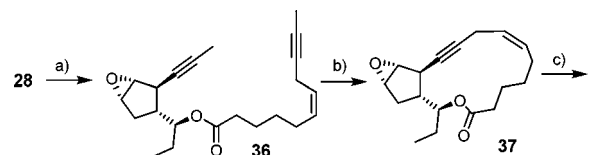
From this point onward, two different routes to **2** were pursued (Scheme 2). Esterification of **20** with 9-undecynoic acid set the stage for the macrocyclization by ring-closing alkyne metathesis (RCAM) of diyne **24**.¹⁵ This key transformation was effected with complex **32** as precatalyst, which was activated in situ as previously outlined.¹⁶ As expected, the catalyst rigorously distinguished between the double- and the triple bonds in **24**, thus emphasizing the notion that alkyne and alkene metatheses are chemically orthogonal; moreover, the labile skipped enyne motif remained intact. Unfortunately, however, oxidation of the olefin in product **25** with dimethyldioxirane provided a 3:1 mixture of isomers; though separable, Lindlar reduction to the resulting (Z)-alkenes revealed that it was the minor epoxide isomer which led to the natural product **2**.

Therefore, the secondary alcohol in **20** was used to direct the epoxidation to the α -face of the olefin. In line with a literature precedent,⁵ catalytic VO(acac)₂ in combination with *t*-BuOOH was most effective,¹⁷ affording product **28** with five contiguous chiral centers in 94% yield as a single isomer. Its subsequent esterification turned out to be challenging, as the oxirane is highly prone to ring-opening. Only the use of carbodiimide **31** escorted by a tosylate anion gave well-reproducible results.

The unusual sensitivity of the epoxide also accounts for the fact that the macrocyclization of the resulting diyne **29** with the aid of complex **32**¹⁶ gave variable yields (50–89%) and required rather high loadings (20–40 mol %), although this precatalyst

had previously been found compatible with oxiranes.¹⁸ The classical tungsten alkylidyne **35** failed completely, likely because of its significant Lewis acidity,¹⁹ whereas precatalyst **33** was unsuitable for the known propensity of the nitride function to react with epoxides.²⁰ Gratifyingly, however, a new generation of molybdenum alkylidyne complexes endowed with Ph₃SiO ligands nicely solved the problem.²¹ Specifically, complex **34** (5 mol %) gave the desired cycloalkyne **30** in 80% yield (the remainder being cyclic dimer). The remarkable performance of **34** is ascribed to the tempered Lewis acidity of its Mo center as well as to the poor nucleophilicity of the peripheral silanolates.²¹ Lindlar reduction of **30** then completed the total synthesis of ecklonialactone B (**2**).

Scheme 3^a



^a Reagents and conditions: (a) undec-6(Z)-en-9-ynoic acid, **31**, DMAP, CH₂Cl₂, 65%; (b) **34** (5 mol %), MS 5 Å, toluene, 90%; (c) P₂Ni (25 mol %), H₂, EtOH, 69%.

As expected, ecklonialactone A (**1**), containing an additional skipped olefin in the lipidic tether, could be obtained analogously, although its epoxide turned out to be even more fragile (Scheme 3). Whereas RCAM of diyne **36** with complex **32** once again gave erratic results, alkylidyne **34** furnished **37** almost quantitatively. Given the unusual sensitivity of this particular substrate, this result bodes well for future applications of **34** and related catalysts.²¹ The final semireduction had to be effected with nickel boride rather than by Lindlar hydrogenation. Since **1** rapidly opens to ecklonialactone C (**3**) or eiseniachloride A (**6**) on treatment with aqueous HClO₄ or HCl, respectively, formal syntheses of these sister compounds have also been accomplished.⁴

Overall, the concise and protecting-group-free entry into this unusual class of marine oxylipins features respectable levels of atom, redox, and step economy and relies, to a notable extent, on catalysis. It bears witness for the power of complex **34**, which sets new standards in the field of alkyne metathesis.²¹ In essence, it is the ability to rigorously distinguish between alkenes and alkynes in oxidative and reductive as well as metathetic maneuvers which forms the chemical basis for the success of this endeavor.

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Supporting Information Available: Experimental section 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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