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Synthesis of Plakortolides E and I Enabled by Base Metal Catalysis

Stefan Leisering, Alexandros Mavroskoufis, Patrick Voßnacker, Reinhold Zimmer, and Mathias Christmann*

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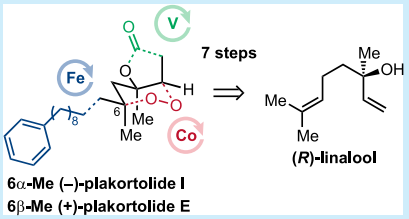
ABSTRACT: A protecting-group-free synthesis of two endoperoxide natural products, plakortolide E and plakortolide I, is reported. Key steps are a vanadium-mediated epoxidation, an iron-catalyzed allylic substitution, and a cobalt-induced endoperoxide formation. Our approach combines chemoselective bond-forming reactions and one-pot operations to forge an overall efficient synthesis.



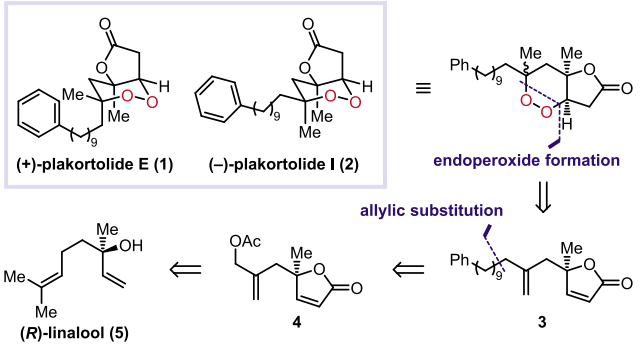
In synthesis planning, it is desirable to derive the target molecule from a carefully selected starting material through a sequence of successive construction steps with minimal functional group interconversions or protecting-group manipulations.[1] The concepts of atom,[2] redox,[3] step,[4] and pot[5] economy provide guidelines to evaluate different synthetic approaches and to design an efficient synthesis.[6] With these considerations in mind, we embarked on developing rapid syntheses of plakortolides E (**1**) and I (**2**) from (*R*)-linalool, a readily available monoterpene with a seven-carbon overlap with the bicyclic core structure of the target including one stereogenic center. Methodologically, we focused on the use of base metal catalysts for some anticipated challenging chemoselective transformations.[7]

Endoperoxides from both terrestrial and marine sources constitute a class of natural products featuring a wide range of unique and often underexplored bioactivities.[8] For instance, several polyketide-derived endoperoxides such as plakinic acids, plakortides, and plakortolides show potential activity as antitumor, antibacterial, and antifungal agents.[9] Furthermore, terpene-based endoperoxides have proven as valuable compounds for combating malaria with artemisinin as the most important lead structure.[10]

The bicyclic 1,2-dioxane-fused butyrolactone plakortolide I (**2**) and its C6-epimer, plakortolide E (**1**), were isolated from marine sponges.[11,12] In 2002, Jung reported the first synthesis of racemic plakortolide I (**2**).[13] Ten years later, Vatèle[14] described an asymmetric synthesis of (−)-plakortolide I (**2**) and (+)-plakortolide E (**1**).

In our retrosynthetic approach, we envisioned a late-stage endoperoxide formation by a tandem Mukaiyama hydroperoxidation/oxa-Michael addition sequence to access either of the two natural products. Installation of the side chain by allylic substitution would simplify both epimeric natural products **1** and **2** retrosynthetically to allyl acetate **4** which we traced back to our starting material **5**. Herein, we report a seven-step synthesis of enantiopure (+)-plakortolide E (**1**) and (−)-plakortolide I (**2**) from commercially available monoterpenoid (*R*)-linalool (**5**) (Scheme 1).

Scheme 1. Retrosynthetic Analysis of (+)-Plakortolide E and (−)-Plakortolide I



The synthesis commenced with the chemoselective vanadium-catalyzed epoxidation of the terminal double bond providing the corresponding epoxide as an inconsequential mixture of two diastereomers (dr 3:2) in 74% yield (see the Supporting Information).[16] Opening of the epoxides with potassium cyanide under acidic conditions afforded nitrile **6** as a mixture of diastereomers (80% yield). Hydrolysis under basic conditions followed by acidic lactonization in an aqueous medium provided the corresponding butyrolactone in 80% yield after isolation (see the Supporting Information). In a subsequent step, elimination of the hydroxyl group was

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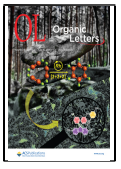

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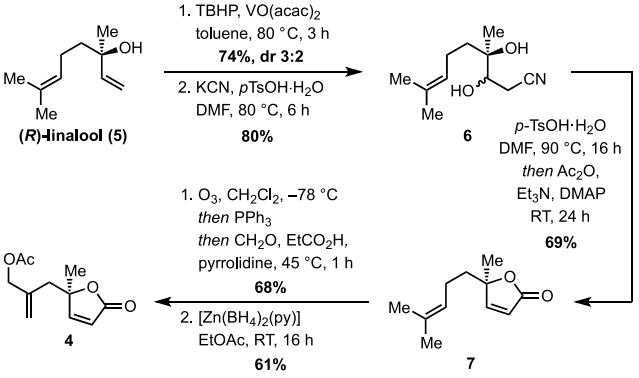
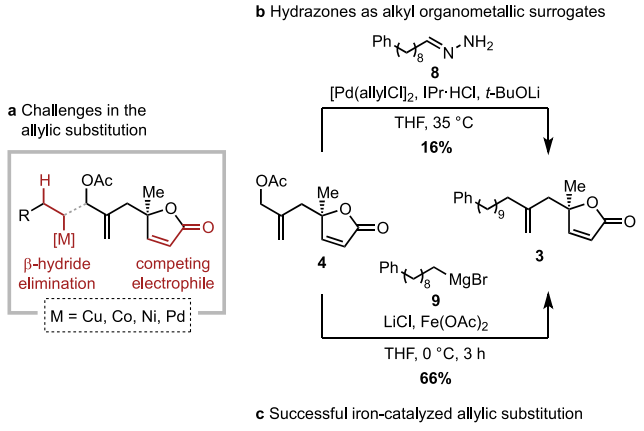
achieved by treatment with acetic anhydride in the presence of triethylamine to give the desired butenolide **7** in 81% yield. Gratifyingly, we found that the hydrolysis and the lactonization step could be combined in a tandem process mediated by *p*-TsOH·H_2O in DMF. Upon treatment with acetic anhydride and triethylamine, elimination of the hydroxyl group was achieved, thus allowing the synthesis of butenolide **7** from nitrile **6** in a one-pot procedure with an overall yield of 69%. Butenolide **7** was subjected to a one-pot ozonolysis/α-methylenation[17] (68% yield). The resulting enal was reduced by pyridine zinc borohydride in ethyl acetate to directly furnish allyl acetate **4** (Scheme 2).[18]

Scheme 2. Synthesis of Allyl Acetate 4



With a precursor for the allylic substitution in hand, we investigated the installation of the side chain. Initial attempts to couple both fragments by cuprate-mediated allylic substitution failed. We recognized a chemoselectivity challenge imposed by the substrate, as it is known that many transition metals catalyze both allylic substitutions and conjugate additions.[19] To shut down the competing pathway, we investigated alternative processes.[20] Although palladium-catalyzed conjugate additions have been reported in recent years,[21] we anticipated that selectivity for the allylic substitution is achievable. However, typical nucleophiles for Tsuji–Trost-type reactions are either heteroatoms or stabilized carbanions, e.g., enolates, deprotonated sulfones and alkynes.[20,22] In contrast, the use of organomagnesium compounds is plagued by β-hydride elimination of the organometallic reagent or umpolung[23] of the π-allyl palladium complex into a nucleophile. When we examined the palladium-catalyzed allylic substitution with diethylzinc, we observed deoxygenation, presumably via β-hydride elimination and subsequent reductive elimination.[24] Although there have been reports by Maulide and co-workers to suppress those competing pathways and promote reductive elimination, their studies were limited to diethylzinc and required non-commercially available ligands.[25] Recently, Li and co-workers described a method for the palladium-catalyzed C-allylation of deprotonated hydrazones as surrogates for nonstabilized carbon nucleophiles.[26] When allyl acetate **4** was treated with hydrazone **8**, the formation of coupling product **3** was observed, albeit in only 16% yield (Scheme 3). Next, we proceeded to investigate approaches involving cobalt, nickel, and iron catalysis as for these metals reactions with nonstabilized nucleophiles are described.[27] Unfortunately, attempts using cobalt and nickel suffered from either no conversion or decomposition. Recently, Jacobi von Wangelin

Scheme 3. Chemoselective Allylic Substitution of 4



and co-workers showed that inexpensive $Fe(OAc)_2$ is an efficient catalyst for the allylic substitution with alkylmagnesium halides under mild conditions.[27e] Their protocol effectively inhibits competing β-hydride elimination without the need of stabilizing ligands or solvents. Initial treatment of allyl acetate **4** with alkylmagnesium bromide **9** in the presence of catalytic amounts of anhydrous $Fe(OAc)_2$ in Et_2O gave no conversion, presumably due to limited solubility. Interestingly, we found that addition of anhydrous LiCl in THF afforded the desired product **3** in 66% yield (Scheme 3).[27e]

Having assembled the carbon skeleton, we addressed the remaining challenge of introducing the endoperoxide. Inspired by the application of cobalt-catalyzed hydrofunctionalizations with oxygen in total synthesis,[28] we anticipated a chemo- and regioselective hydroperoxidation of olefin **3** followed by an oxa-Michael addition in a tandem process to furnish both natural products **1** and **2**. Based on the conditions employed by Vatèle and Barnych, we treated **3** with Et_3SiH and $Co(thd)_2$ in vigorously oxygen-saturated 1,2-dichloroethane.[14] Surprisingly, these conditions did not result in the conversion of the starting material even at prolonged reaction time or elevated temperature. We found that addition of protic solvents such as *i*-PrOH facilitated the conversion of olefin **3** which avoided undesired side reactions.[14] Under these conditions, the direct formation of endoperoxides **1** and **2** was observed, but was accompanied by decomposition of the products resulting in low isolated yields. Although decomposition reactions could be suppressed at 0 °C, the oxa-Michael addition was slowed and the intermediate was partially trapped as the corresponding silyl peroxide. This drawback was circumvented by in situ desilylation with TBAF in the presence of TFE (2,2,2-trifluoroethanol) to buffer the enolate resulting from the oxa-Michael reaction, thereby avoiding potential Weitz–Scheffer-type epoxidation.[14,15] This tandem endoperoxide formation afforded (−)-plakortolide I (**2**) in 42% yield, along with its C6-epimer (+)-plakortolide E (**1**) in 35% yield. Single crystals of **1** were grown and analyzed by X-ray analysis, thereby confirming the structure and absolute configuration of **1** and indirectly of **2** (Scheme 4).

To illustrate the efficiency of our synthesis, we applied a color-coded flowchart representation that was recently developed by our group (Figure 1).[6c] More than half of the transformations are strategic bond forming reactions that utilize all of the functional groups given by the chiral terpene starting material **5**. Two functional group interconversions

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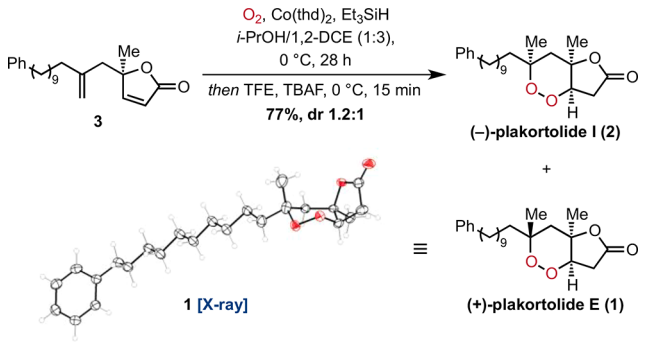
Scheme 4. Tandem Endoperoxide Formation for the Synthesis of (+)-Plakortolide E and (−)-Plakortolide I[a]



[a]Thermal ellipsoids at 50% probability; disorder was omitted for clarity.

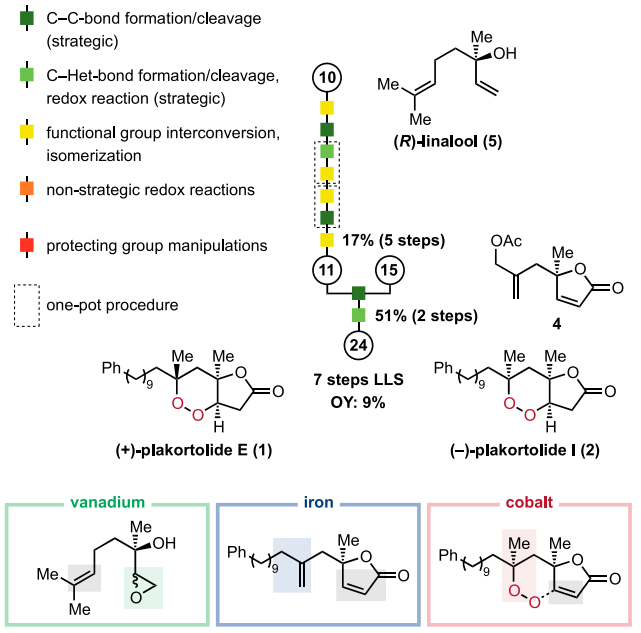


Figure 1. Flowchart representation of the synthesis of (+)-plakortolide E (**1**) and (−)-plakortolide I (**2**).

were combined with constructive bond formations in one-pot procedures to enhance the pot economy of the synthesis.

In conclusion, we have developed a concise synthesis of enantiopure (+)-plakortolide E (**1**) and (−)-plakortolide I (**2**) from commercially available (*R*)-linalool (**5**). By using $Fe(OAc)_2$ as catalyst, a chemoselective installation of the alkyl side chain was achieved in good yield.[29] This work demonstrates that a straightforward and protecting-group-free synthesis of endoperoxide natural products can be fueled by chemoselective transformations with earth-abundant transition-metal catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01457.

Experimental procedures and spectroscopic data (PDF)

Accession Codes

CCDC 2074855 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Mathias Christmann − *Institute of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany;* orcid.org/0000-0001-9313-2392; Email: mathias.christmann@fu-berlin.de

Authors

Stefan Leisering − *Institute of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Alexandros Mavroskoufis − *Institute of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Patrick Voßnacker − *Institute of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Reinhold Zimmer − *Institute of Chemistry and Biochemistry, Freie Universität Berlin, 14195 Berlin, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01457

Notes

The authors declare no competing financial interest.

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(29) A version of this research was previously posted to ChemRxiv (2021-04-29): Leisering, S.; Mavroskoufis, A.; Voßnacker, P.; Zimmer, R.; Christmann, M. Synthesis of Plakortolides E and I Enabled by Base Metal Catalysis. *ChemRxiv* **2021**, DOI: 10.26434/chemrxiv.14501505.v1.

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