Synthesis of Plakortolides E and I Enabled by Base Metal Catalysis

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

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany

Supporting Information Placeholder

ABSTRACT: A protecting-group-free synthesis of two endoperoxide natural products, plakortolide E and plakortolide I, is reported. Key-steps feature the use of earth-abundant transition metals, consisting of a vanadium-mediated epoxidation, an iron-catalyzed allylic substitution, and a cobalt-induced endoperoxide formation. Our approach combines redox-economy, chemoselective bond-forming reactions, and telescoping into one-pot operations to forge an overall efficient synthesis.

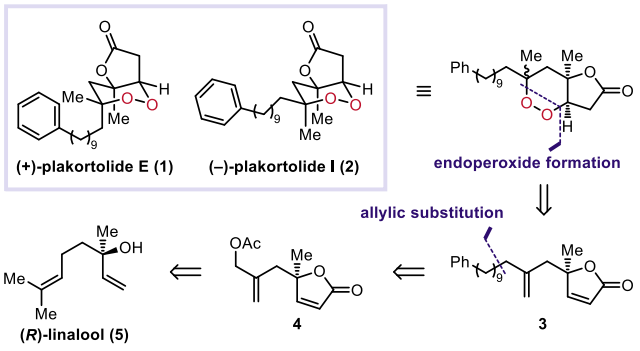
In synthesis planning, it is desirable to derive the target molecule from a carefully selected starting material through a sequence of successive construction steps with minimal functional group interconversions or protecting-group manipulations.[1] The concepts of atom,[2] redox,[3] step[4] and pot[5] 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 and I from (*R*)-linalool, a readily available monoterpene with a seven-carbon overlap to 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 the (–)-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).

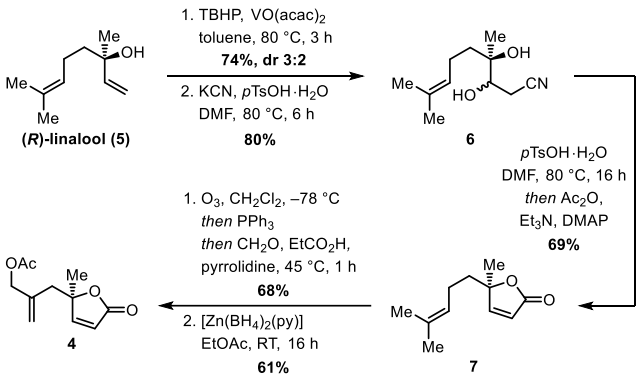
Scheme 1. Retrosynthetic Analysis of (+)-Plakortolide E and (–)-Plakortolide I



The synthesis commenced with the chemoselective vanadium-catalyzed epoxidation of the terminal double bond providing the corresponding epoxide as an inconsequential mixture of both diastereomers (dr 3:2) in 74% yield (see Supporting Information).[15] Opening of the epoxides with potassium cyanide under acidic conditions afforded both diastereomers of nitrile **6** (80% yield). Hydrolysis under basic conditions followed by acidic lactonization in an aqueous medium provided the corresponding butyrolactone in 80% yield after isolation (see Supporting Information). In a subsequent step,

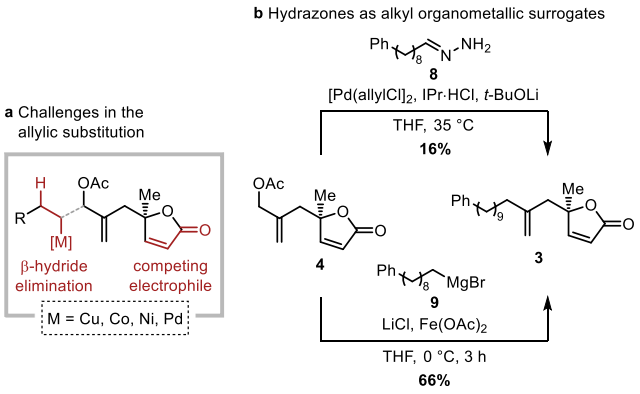
eliminiation of the hydroxyl group was achieved by treatment with acetic anhydride in the presence of triethylamine to give the desired butenolide **7** in 81% yield. Gratifyingly, we found that the hydrolysis and the lactonization step could be combined in a tandem process mediated by *p*TsOH·H_2O in DMF. Upon treatment with acetic anhydride and triethylamine, elimination of the hydroxyl group could be 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[16] (68% yield). The resulting enal was reduced by pyridine zinc borohydride in ethyl acetate to directly furnish allyl acetate **4**.[17]

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.[18] To shut down the competing pathway, we investigsted alternative processes.[19] Although palladium-catalyzed conjugate additions have been reported in recent years,[20] 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.[19,21] In contrast, the use of organomagnesium compounds is plagued by β-hydride elimination of the organometallic reagent or umpolung[22] 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.[23] Although there have been reports by Maulide and coworkers to suppress those competing pathways and promote reductive elimination, their studies were limited to diethylzinc and required non-commercially available ligands.[24] Recently Li and coworkers described a method for the palladium-catalyzed C-allylation of deprotonated hydrazones as surrogates for non-stabilized carbon nucleophiles.[25] 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 non-stabilized nucleophiles are described.[26] Unfortunately, attempts using cobalt and nickel suffered from either no conversion or decomposition. Recently, Jacobi von Wangelin and coworkers showed that inexpensive $Fe(OAc)_2$ is an efficient catalyst for the allylic substitution with alkylmagnesium halides under mild conditions.[26e] 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 $Fe(OAc)_2$ in Et_2O gave no conversion, presumably due to limited solubility. Interstingly, we found that addition of LiCl in THF afforded the desired product **3** in 66% yield (Scheme 3).[26e]

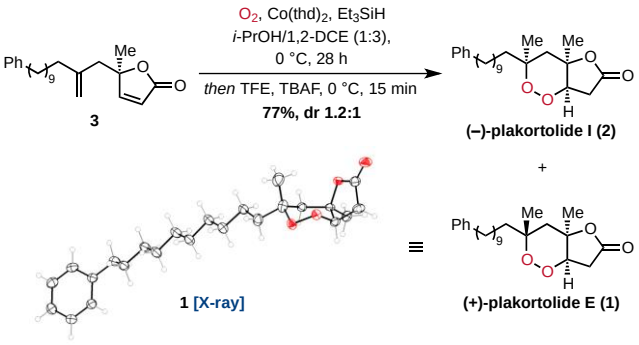
Scheme 3. Chemoselective Allylic Substitution of 4



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,[27] 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**. Unfortunately, Mukaiyama-Isayama hydroperoxidation of **3** with Et_3SiH and $Co(thd)_2$ in vigorously oxygen saturated 1,2-DCE at ambient temperature resulted in no conversion even at prolonged reaction time or elevated temperature.[14] However, addition of protic solvents such as *i*-PrOH facilitated the conversion. 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 down 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] 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).

Scheme 4. Tandem Endoperoxide Formation for the Synthesis of (+)-Plakortolide E and (–)-Plakortolide I (Thermal Ellipsoids at 50% Probability; Disorder Was Obmitted for Clarity)



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 the functional groups given by the chiral terpene starting material **5**. Two functional group interconversions were combined with constructive bond formations in one-pot procedures to enhance the pot economy of the synthesis.

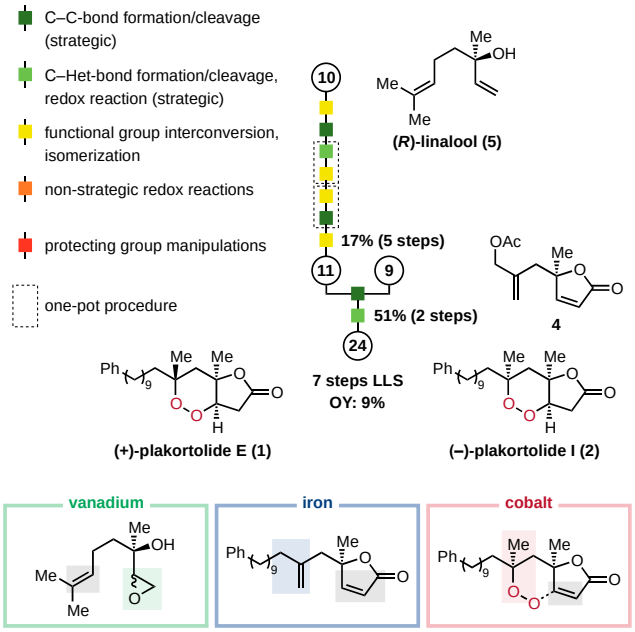


Figure 1. Flowchart representation of the synthesis of (+)-plakortolide E (**1**) and (–)-plakortolide I (**2**).

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 an $Fe(OAc)_2$ catalyst, a chemoselective installation of the alkyl side chain was achieved in good yield. 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 on the ACS Publications website.
X-ray crystallographic data for **1** (CIF)
Experimental procedures and spectroscopic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: mathias.christmann@fu-berlin.de

ORCID

Mathias Christmann: 0000-0001-9313-2392

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Luise Schefzig for preparative support and Merlin Kleoff (both Freie Universität Berlin) for helpful discussions.

REFERENCES

(1) Hendrickson, J. B. Systematic Synthesis Design. IV. Numerical codification of construction reactions. *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800.

(2) (a) Trost, B. M. The atom economy – a search for synthetic efficiency. *Science* **1991**, *254*, 1471–1477. (b) Trost, B. M. Atom Economy – A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

(3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox economy in organic synthesis. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867.

(4) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008**, *41*, 40–49. (b) Wender, P. A.; Miller, B. L. Synthesis at the molecular frontier. *Nature* **2009**, *460*, 197–201.

(5) (a) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866–880. (b) Hayashi, Y. Time and Pot Economy in Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 1385–1398.

(6) (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021. (b) Gaich, T.; Baran, P. S. Aiming for the Ideal Synthesis. *J. Org. Chem.* **2010**, *75*, 4657–4673. (c) Schwan, J.; Christmann, M. Enabling strategies for step efficient syntheses. *Chem. Soc. Rev.* **2018**, *47*, 7985–7995.

(7) (a) Zweig, J. E.; Kim, D. K.; Newhouse, T. R. Methods Utilizing First-Row Transition Metals in Natural Product Total Synthesis. *Chem. Rev.* **2017**, *117*, 11680–11752. (b) Beaumier, E. P.; Pearce, A. J.; See, X. Y.; Tonks, I. A. Modern applications of low-valent early transition metals in synthesis and catalysis. *Nat. Chem. Rev.* **2019**, *3*, 15–34. (c) Bullock, R. M.; Chen, J. G.; Gagliardi, L.; Chirik, P. J.; Farha, O. K.; Hendon, C. H.; Jones, C. W.; Keith, J. A.; Klosin, J.; Minteer, S. D.; Morris, R. H.; Radosevich, A. T.; Rauchfuss, T. B.; Strotman, N. A.; Vojvodic, A.; Ward, T. R.; Yang, J. Y.; Surendranath, Y. Using nature's blueprint to expand catalysis with Earth-abundant metals. *Science* **2020**, *369*, eabc3183.

(8) Bu, M.; Yang, B. B.; Hu, L. Natural Endoperoxides as Drug Lead Compounds. *Curr. Med. Chem.* **2016**, *23*, 383–405.

(9) (a) Dembitsky, V. M.; Gloriozova, T. M.; Poroikov, V. V. Natural Peroxy Anticancer Agents. *Mini Rev. Med. Chem.* **2007**, *7*, 571–589. (b) Dembitsky, V. M. Bioactive peroxides as potential therapeutic agents. *Eur. J. Med. Chem.* **2008**, *43*, 223–251.

(10) (a) Tu, Y. Artemisinin–A Gift from Traditional Chinese Medicine to the World (Nobel Lecture). *Angew. Chem. Int. Ed.* **2016**, *55*, 10210–10226. (b) Wang, J.; Xu, C.; Wong, Y. K.; Li, Y.; Liao, F.; Jiang, T.; Tu, Y. Artemisinin, the Magic Drug Discovered from Traditional Chinese Medicine. *Engineering.* **2019**, *5*, 32–39.

(11) Qureshi, A.; Salvà, J.; Harper, M.; Faulkner, D. J. New Cyclic Peroxides from the Philippine Sponge *Plakinastrella* sp. *J. Nat. Prod.* **1998**, *61*, 1539–1542.

(12) (a) Rudi, A.; Afanii, R.; Gravalos, L. G.; Aknin, M.; Gaydou, E.; Vacelet, J.; Kashman, Y. Three New Cyclic Peroxides from the Marine Sponge *Plakortisaff simplex*. *J. Nat. Prod.* **2003**, *66*, 682–685. (b) Correction of the initially assigned structure to (+)-plakortolide E: .Plakortolide Stereochemistry Revisited: Yong, K. W. L.; Barnych, B.; De Voss. J. J.; Vatèle, J.-M.; Garson, M. J. The Checkered History of Plakortolides E and I. *J. Nat. Prod.* **2012**, *75*, 1792–1797.

(13) Jung, M.; Ham, J.; Song, J. First Total Synthesis of Natural 6-Epiplakortolide E. *Org. Lett.* **2002**, *16*, 2763–2765.

(14) Barnych, B.; Vatèle, J.-M. Total Synthesis of *seco*-Plakortolide E and (–)-*ent*-Plakortolide I: Absolute Configurational Revision of Natural Plakortolide I. *Org. Lett.* **2012**, *14*, 564–567.

(15) Langhanki, J.; Rudolph, K.; Erkel, G.; Opatz, T. Total synthesis and biological evaluation of the natural product (−)-cyclonerodiol, a new inhibitor of IL-4 signaling. *Org. Biomol. Chem.* **2014**, *12*, 9707–9715.

(16) Benohoud, M.; Erkkilä, A.; Pihko, P. M. ORGANOCATALYTIC – METHYLENATION OF ALDEHYDES: PREPARATION OF 3,7-DIMETHYL-2-METHYLENE-6-OCTENAL. *Org. Synth.* **2010**, *87*, 201–208.

(17) Zeynizadeh, B.; Setamdideh, D.; Faraji, F. Reductive Acetylation of Carbonyl Compounds to Acetates with Pyridine Zinc Borohydride. *Bull. Korean Chem. Soc.* **2008**, *29*, 76–80.

(18) (a) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. *Chem. Rev.* **2008**, *108*, 2796–2823. (c) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170–3387. (d) Butt, N. A.; Zhang, W. Transition metal-catalyzed allylic substitution reactions with unactivated allylic substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929–7967.

(19) (a) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921–2944. (b) Lu, Z.; Ma, S. Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis. *Angew. Chem. Int. Ed.* **2007**, *47*, 258–297.

(20) (a) Cacchi, S.; Misiti, D.; Palmieri, G. The palladium-catalysed conjugate addition type reaction of arylmercury compounds with α,β-unsaturated ketones in a two-phase system. *Tetrahedron* **1981**, *37*, 2941–2946. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. Conjugate Addition of Aryl Boronic Acids to Enones Catalyzed by Cationic Palladium(II)-Phosphane Complexes. *Angew. Chem. Int. Ed.* **2003**, *42*, 2768–2770. (c) Gutnov, A. Palladium-Catalyzed Asymmetric Conjugate Addition of Aryl-Metal Species. *Eur. J. Org. Chem.* **2008**, 4547–4554. (d) Lin, S.; Lu, X. Cationic Pd(II)/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to β,β-Disubstituted Enones: Construction of Quaternary Carbon Centers. *Org. Lett.* **2010**, *12*, 2536–2539. (e) Gottumukkala, A. L.; Matcha, K.; Lutz, M.; de Vries, J. G., Minnaard, A. J. Palladium-Catalyzed Asymmetric Quaternary Stereocenter Formation. *Chem. Eur. J.* **2012**, *18*, 6907–6914. (f) Chen, W.; Chen, H.; Xiao, F.; Deng, G.-J. Palladium-catalyzed conjugate addition of arylsulfonyl hydrazides to α,β-unsaturated ketones. *Org. Biomol. Chem.* **2013**, *11*, 4295–4298.

(21) (a) Weaver, J. D.; Tunge, J. A. Decarboxylative Allylation using Sulfones as Surrogates of Alkanes. *Org. Lett.* **2008**, *10*, 4657–4660. (b) Trost, B. M.; Zhang, T.; Sieber, J. D. Catalytic asymmetric allylic alkylation employing heteroatom nucleophiles: a powerful method for C–X bond formation. *Chem. Sci.* **2010**, *1*, 427–440. (c) Li, Y.-X.; Xuan, Q.-Q., Liu, L.; Wang, D.; Chen, Y.-J.; Li, C.-J. A Pd(0)-Catalyzed Direct Dehydrative Coupling of Terminal Alkynes with Allylic Alcohols To Acces 1,4-Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 12536–12539. (d) Akkarasamiyo, S.; Sawadjoon, S.; Orthaber, A.; Samec, J. S. M. Tsuji-Trost Reaction of Non-Derivatized Allylic Alcohols. *Chem. Eur. J.* **2018**, *24*, 3488–3498.

(22) (a) Tamaru, Y.; Tanaka, A., Yasui, K.; Goto, S.; Tanaka, S. Highly Stereoselective Allylation of Benzaldehyde: Generation of a Stereochemically Defined Allylzinc Species from a π-Allylpalladium Intermediate and Diethylzinc. *Angew. Chem. Int. Ed.* **1995**, *34*, 787–789. (b) Howell, G. P.; Minnaard, A. J.; Feringa, B. L. Asymmetric allylation of aryl aldehydes: studies on the scope and mechanism of the palladium catalyzed diethylzinc mediated umpolung using phosphoramidite ligands. *Org. Biomol. Chem.* **2006**, *4*, 1278–1283. (c) Spielmann, K.; Niel, G.; de Figueiredo, R. M.; Campagne, J.-M. Catalytic nucleophilic 'umpoled' π-allyl reagents. *Chem. Soc. Rev.* **2018**, *47*, 1159–1173.

(23) (a) Yuan, K.; Scott, W. J. On the mechanism of the reduction of primary halides with Grignard reagents in the presence of (dppf)PdCl2 or (dppf)Pd(0). *J. Org. Chem.* **1990**, *55*, 6188–6194. (b) Fukuda, J.-i.; Nogi, K.; Yorimitsu, H. Cobalt-Catalyzed Reduction of

Aryl Sulfones to Arenes by Means of Alkylmagnesium Reagents. *Asian J. Org. Chem.* **2018**, *7*, 2049–2052.

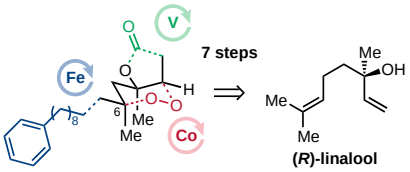
(24) Misale, A.; Niyomchon, S.; Luparia, M.; Maulide, N. Asymmetric Palladium-Catalyzed Allylic Alkylation Using Dialkylzinc Reagents: A Remarkable Ligand Effect. *Angew. Chem. Int. Ed.* **2014** *53*, 7068–7073.

(25) Zhu, D.; Lv, L.; Li, C.-C.; Ung, S.; Gaom, J.; Li, C.-J. Umpolung of Carbonyl Groups as Alkyl Organometallic Reagent Surrogates for Palladium-Catalyzed Allylic Alkylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 16520–16524.

(26) (a) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. Cobalt-Catalyzed Reductive Allylation of Alkyl Halides with Allylic Acetates or Carbonates. *Angew. Chem. Int. Ed.* **2011**, *50*, 10402–10405. (b) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Grignard Reagents and Identification of Selective Anti-Breast-Cancer Agents. *Angew. Chem. Int. Ed.* **2014**, *53*, 2422–2427. (c) Yang, B.; Wang, Z.-X. Nickel-Catalyzed Alkylation or Reduction of Allylic Alcohols with Alkyl Grignard Reagents. *J. Org. Chem.* **2020**, *85*, 4772–4784. (d) Cahiez, G.; Avedissian, H. Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds. *Synthesis* **1998**, 1199–1205. (e) Bernauer, J.; Wu, G.; Jacobi von Wangelin, A. Iron-catalysed allylation-hydrogenation sequence as masked alkyl-alkyl cross-couplings. *RSC Adv.* **2019**, *9*, 31217–31223.

(27) (a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. Oxidation-Reduction Hydration of Olefins with Molecular Oxygen and 2-Propanol Catalyzed by Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 449–452. (b) Isayama, S.; Mukaiyama, T. Novel Method for the Preparation of Triethylsilyl Peroxides from Olefins by the Reaction with Molecular Oxygen and Triethylsilane Catalyzed by Bis(1,3-diketonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 573–576. (c) Isayama, S. An Efficient Method for the Direct Peroxygenation of Various Olefinic Compounds with Molecular Oxygen and Triethylsilane Catalyzed by a Cobalt(II) Complex. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305–1310. (d) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefines. *Chem. Rev.* **2016**, *116*, 8912–9000.

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.



6a-Me (–)-plakortolide I
6b-Me (+)-plakortolide E

(*R*)-linalool

Synthesis of Plakortolides E and I Enabled by Base Metal Catalysis

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

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany

Supporting Information

Table of Content

1. General Information

1.1 Materials and Methods

Reactions with air or moisture sensitive substances were carried out under an argon atmosphere using standard Schlenk technique. Ambient or room temperature (RT) refers to 18–23 °C.

Unless otherwise noted, all staring materials and reagents were purchased from commercial distributors and used without further purification. Anhydrous dichloromethane, tetrahydrofuran and toluene were provided by purification with a MBraun SPS-800 solvent system (BRAUN) using solvents of HPLC grade purchased from FISCHER Scientific and ROTH. Anhydrous *N*,*N*-dimethylformamide and 1,2-Dichloroethane (99.8+%) were purchased from ACROS Organics. HPLC-grade 2-propanol was purchased from VWR. Triethylamine was distilled from calcium hydride and stored under argon over KOH. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use.

Column chromatography was performed on silica 60 M (0.040-0.063 mm, 230-400 mesh, MACHEREY-NAGEL).

Medium pressure liquid chromatography (MPLC) was performed with a TELEDYNE ISCO Combi-Flash Rf200 using prepacked silica columns and cartridges from TELDYNE. UV response was monitored at 254 nm and 280 nm. As eluents, cyclohexane (99.5+% quality) and EtOAc (HPLC grade) were used.

The following compounds were prepared according to the literature: **SI-1**,[1] pyridine zinc borohydride,[2] 9-phenylnonanal,[3] (9-bromononyl)benzene.[4]

1.2 Analysis

Reaction monitoring: Reactions were monitored by thin layer chromatography (TLC). TLC-analysis was performed on silica gel coated aluminum plates ALUGRAM® Xtra SIL G/UV_{254} purchased from MACHEREY-NAGEL. Products were visualized by UV light at 254 nm and by using staining reagents (based on $KMnO_4$ and anisaldeyhde).

NMR spectroscopy: ^{1}H NMR and ^{13}C NMR spectral data were recorded on JEOL (ECX 400, ECP 500) and BRUKER (AVANCE III 500, AVANCE III 700) spectrometer in the reported deuterated solvents. The chemical shifts (δ) are listed in parts per million (ppm) and are reported relative to the corresponding residual non-deuterated solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Integrals are in accordance with assignments; coupling constants (*J*) are given in Hz. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), br = broad and combinations thereof. In the case where no multiplicity could be identified, the chemical shift range of the signal is given as m (multiplet). ^{13}C NMR spectra are ^{1}H-broadband decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC).

High resolution mass spectrometry: High resolution mass spectra (HRMS) were measured with an AGILENT 6210 ESI-TOF (10 µL/min, 1.0 bar, 4 kV) instrument.

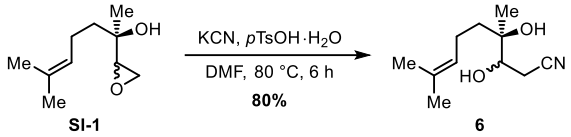
Optical rotation: Optical rotation values were measured with a JACSO P-2000 polarimeter at 589 nm using 100 mm cells and the indicated solvent and concentration (g/100 mL) at the given temperatures.

Melting points: Melting points were determined by a digital melting point apparatus (Büchi B-545) and are uncorrected.

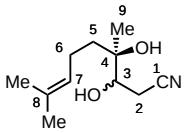
X-ray: X-ray diffraction data was collected on a BRUKER D8 Venture CMOS area detector (Photon 100) diffractometer with $Cu_{K\alpha}$ radiation. Single crystals were coated with perfluoroether oil and mounted on a 0.2 mm Micromount. The structures were solved with the ShelXT[5] structure solution program using intrinsic phasing and refined with the ShelXL[6] refinement package using least squares on weighted F2 values for all reflections using OLEX2.[7]

2. Experimental Procedures and Analytical Data

2.1 (4*R*)-3,4-Dihydroxy-4,8-dimethylnon-7-enenitrile (6)



To a flame-dried Schlenk flask containing a suspension of potassium cyanide (5.02 g, 77.0 mmol, 2.5 equiv) and *para*-toluenesulfonic acid monohydrate (7.04 g, 37.0 mmol, 1.2 equiv) in anhydrous *N*,*N*-dimethylformamide (50 mL) under an argon atmosphere was added a solution of diastereomeric (dr (2*S*, 3*R*):(2*R*, 3*R*)) = 3:2) epoxide **SI-1** (5.25 g, 30.8 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (10 mL) at 40 °C. The resulting mixture was heated to 80 °C and stirred for 6 h. TLC analysis indicated complete consumption of the starting material. After cooling to 0 °C, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL). The mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 4:1 to 2:1) to afford nitrile **6** (4.88 g, 24.7 mmol, 80%) as a colorless oil.

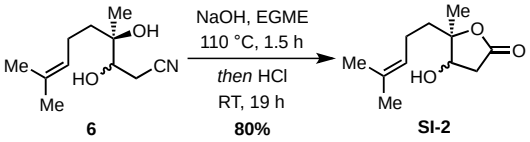


^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.14 (s, 1.2H, H-9$_R$), 1.21 (s, 1.8H, H-9$_S$), 1.35 – 1.44 (m, 0.6H, H-5$_S$), 1.51 – 1.59 (m, 1.4H, H-5$_S$, H-5$_R$), 1.62 (s, 3H, Me), 1.68 (s, 3H, Me), 1.99 – 2.15 (m, 2H, H-6), 2.52 – 2.65 (m, 1H, H-2), 3.73 – 3.83 (m, 1H, H-3), 5.06 – 5.12 (m, 1H, H-7) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 17.81 (Me$_R$), 17.83 (Me$_S$), 21.1 (C-2$_S$), 21.2 (C-2$_R$), 21.7 (C-9$_R$), 22.1 (C-6$_S$), 22.3 (C-6$_R$), 22.6 (C-9$_S$), 25.8 (Me), 37.4 (C-5$_S$), 38.5 (C-5$_R$), 72.7 (C-3$_R$), 73.3 (C-3$_S$), 74.18 (C-4$_R$), 74.20 (C-4$_S$), 119.0 (C-1$_R$), 119.2 (C-1$_S$), 123.79 (C-7$_S$), 123.81 (C-7$_R$), 132.6 (C-8$_R$), 132.8 (C-8$_S$) ppm.

HRMS (ESI, pos.): *m*/*z* calcd for $C_{11}H_{19}NO_2Na^+$ [M+Na$^+$]: 220.1308, found 220.1328.

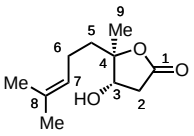
2.2 (5*R*)-4-Hydroxy-5-methyl-5-(4-methylpent-3-ene-1-yl)oxolan-2-one (SI-2)



A solution of nitrile **6** (4.80 g, 24.3 mmol, 1.00 equiv) in ethylene glycol monomethyl ether (25 mL) and aqueous 2 M NaOH (66 mL) was heated to 110 °C and stirred for 1.5 h. After cooling to 0 °C, aqueous 2 M HCl (80 mL) was added until a pH of 2 was reached. The cooling bath was removed and the reaction mixture was stirred for a further 19 h. The solution was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 3:1 to 2:1) to afford lactone **SI-2** (3.84 g, 19.3 mmol, 80%) as a colorless oil.

Both diastereomers could by separated by column chromatography to obtain analytically pure samples which were used for the characterization.

***trans*-Lactone SI-2 (major diastereomer)**



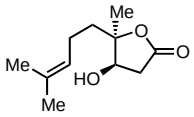
$[\alpha]_D^{22}$ = +2.6 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.39 (s, 3H, H-9), 1.59 (s, 3H, Me), 1.57 – 1.66 (m, 2H, H-5), 1.67 (s, 3H, Me), 2.04 – 2.11 (m, 2H, H-6), 2.54 (dd, *J* = 18.0, 4.4 Hz, 1H, H-2), 2.84 (d_{br}, *J* = 4.8 Hz, 1H, OH), 2.89 (dd, *J* = 18.0, 6.9 Hz, 1H, H-2), 4.20 – 4.29 (m, 1H, H-3), 5.02 – 5.08 (m, 1H, H-7) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 17.8 (Me), 18.6 (C-9), 22.5 (C-6), 25.7 (Me), 38.2 (C-2), 39.4 (C-5), 72.6 (C-3), 90.2 (C-4), 123.1 (C-7), 132.9 (C-8), 175.2 (C-1) ppm.

HRMS (ESI, pos.): *m*/*z* calcd for $C_{11}H_{18}O_3Na^+$ [M+Na$^+$]: 221.1148, found 221.1146.

***cis*-Lactone SI-2 (minor diastereomer)**



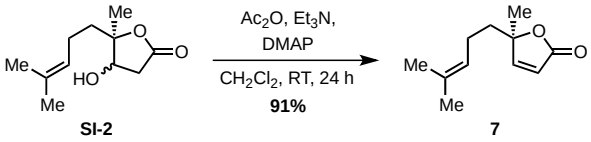
$[\alpha]_D^{21}$ = +21.3 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.33 (s, 3H, H-9), 1.61 (s, 3H, Me), 1.68 (s, 3H, Me), 1.77 (ddd, *J* = 14.0, 10.2, 6.7 Hz, 1H, H-5), 1.83 (ddd, *J* = 14.0, 9.8, 6.1 Hz, 1H, H-5), 2.05 – 2.16 (m, 2H, H-6), 2.50 (dd, *J* = 18.1, 2.4 Hz, 1H, H-2), 2.78 (d_{br}, *J* = 4.7 Hz, 1H, OH), 2.93 (dd, *J* = 18.1, 6.2 Hz, 1H, H-2), 4.15 – 4.20 (m, 1H, H-3), 5.10 – 5.17 (m, 1H, H-7) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 17.8 (Me), 22.5 (C-6), 23.2 (C-9), 25.8 (Me), 34.1 (C-5), 38.6 (C-2), 74.6 (C-3), 90.0 (C-4), 123.5 (C-7), 133.0 (C-8), 175.5 (C-1) ppm.

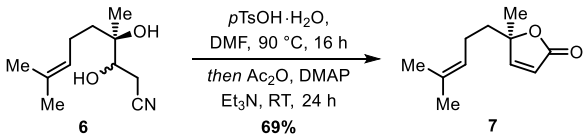
The spectroscopic data is in accordance with the literature.[8]

2.3 (5*R*)-5-Methyl-5-(4-methylpent-3-ene-1-yl)-3-oxolen-2-one (7)



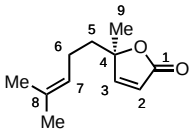
To a flame-dried Schlenk flask containing a solution of lactone **SI-2** (3.65 g, 18.4 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (26 mL) under an argon atmosphere were added Ac_2O (6.97 mL, 74.1 mmol, 4.0 equiv), Et_3N (25.7 mL, 185 mmol, 10 equiv) and 4-(dimethylamino)pyridine (112 mg, 917 µmol, 5 mol%). The reaction mixture was stirred for 24 h at ambient temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL), the layers were seperated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 4:1) to afford butenolide **7** (3.01 g, 16.7 mmol, 91%) as a colorless oil.

One-pot procedure from nitrile 6



A solution of diastereomeric nitrile **7** (293 mg, 1.49 mmol, 1.0 equiv) and *para*-toluenesulfonic acid monohydrate (2.83 g, 14.9 mmol, 10 equiv) in anhydrous *N*,*N*-dimethylformamide (6 mL) under an argon atmosphere was heated to 90 °C and stirred for 16 h. After TLC analysis indicated complete consumption

of the starting material, Ac_2O (2.81 mL, 29.7 mmol, 20 equiv), 4-(dimethylamino)pyridine (36.3 mg, 297 µmol, 20 mol%) and Et_3N (4.12 mL, 29.7 mmol, 20 equiv) were added and stirring was continued for 24 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), the layers were seperated and the aqueous phase was extracted with Et_2O (5 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 4:1) to afford butenolide **7** (186 mg, 1.03 mmol, 69%) as a colorless oil.



$[\alpha]_D^{20}$ = –95.6 (*c* = 1.00, $CHCl_3$).

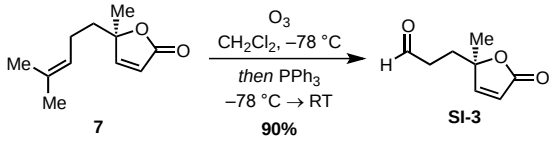
^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.46 (s, 3 H, H-9), 1.56 – 1.57 (m, 3 H, Me), 1.66 – 1.67 (m, 3 H, Me), 1.72 (ddd, *J* = 14.0, 10.7, 5.2 Hz, 1 H, H-5), 1.85 (ddd, *J* = 14.0 Hz, 10.5, 5.4 Hz, 1 H, H-5), 1.88 – 1.94 (m, 1 H, H-6), 1.96 – 2.03 (m, 1 H, H-6), 5.00 – 5.04 (m, 1 H, H-7), 6.00 (d, *J* = 5.6 Hz, 1 H, H-2), 7.34 (d, *J* = 5.6 Hz, 1 H, H-3) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 17.8 (Me), 22.6 (C-6), 24.2 (C-9), 25.8 (Me), 38.4 (C-5), 89.0 (C-4), 120.6 (C-2), 123.0 (C-7), 132.9 (C-8), 160.4 (C-3), 172.7 (C-1) ppm.

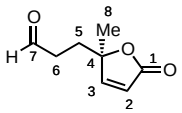
HRMS (ESI, pos.): *m*/*z* calcd for $C_{11}H_{16}O_2K^+$ [M+K$^+$]: 219.0782, found 219.0793.

The spectroscopic data is in accordance with the literature.[9]

2.4 (5*R*)-5-Methyl-5-(3-oxoprop-1-yl)-3-oxolen-2-one (SI-3)



A solution of butenolide **7** (1.40 g, 7.77 mmol, 1.0 equiv) in CH_2Cl_2 (77 mL) was cooled to –78 °C and a stream of ozone was passed through until a blue colour persisted. The excess ozone was then removed by saturating the solution with oxygen until the blue colour faded and triphenylphosphine (2.44 g, 9.30 mmol, 1.2 equiv) was added. The cooling bath was removed and the reaction mixture was warmed to ambient temperature. The crude solution was dry-loaded onto silica and purified by column chromatography (SiO_2, pentane/EtOAc, 4:1 to 1:1 to 0:1) to afford aldehyde **SI-3** (1.08 g, 7.00 mmol, 90%) as a colorless oil.



$[\alpha]_D^{22}$ = –51.1 (*c* = 1.00, $CHCl_3$).

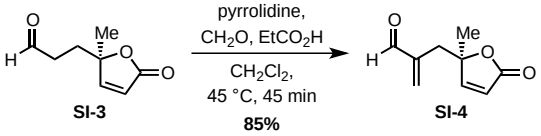
^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.48 (s, 3H, H-8), 2.08 (ddd, *J* = 14.6, 8.2, 6.5 Hz, 1H, H-5), 2.15 (ddd, *J* = 14.6, 8.1, 6.0 Hz, 1H, H-5), 2.39 (dddd, *J* = 18.7, 8.1, 6.5, 0.9 Hz, 1H, H-6), 2.50 (dddd, *J* = 18.7, 8.2, 6.0, 0.9 Hz, 1H, H-6), 6.01 (d, *J* = 5.6 Hz, 1H, H-2), 7.31 (d, *J* = 5.6 Hz, 1H, H-3), 9.71 (t, *J* = 0.9 Hz, 1H, H-7) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.3 (C-8), 29.7 (C-5), 38.0 (C-6), 87.8 (C-4), 121.0 (C-2), 160.0 (C-3), 172.2 (C-1), 200.5 (C-7) ppm.

HRMS (ESI, pos.): *m*/*z* calcd for $C_8H_{10}O_3Na^+$ [M+Na$^+$]: 177.0522, found 177.0515.

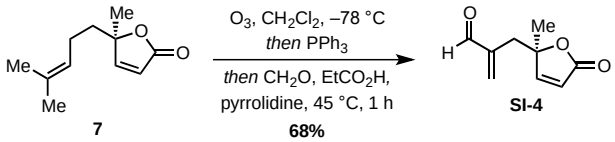
The spectroscopic data is in accordance with the literature.[9]

2.5 (5*R*)-5-Methyl-5-(2-methylene-3-oxoprop-1-yl)-3-oxolen-2-one (SI-4)

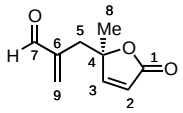


Enal **SI-4** was prepared in analogy to a reported procedure by PIHKO et al. for the α-methylenation of aldehydes.[10] A solution of aldehyde **SI-3** (500 mg, 3.24 mmol, 1.0 equiv), aqueous formaldehyde (37 wt%, 362 µL, 4.87 mmol, 1.5 equiv), propionic acid (24.0 µL, 324 µmol, 10 mol%) and pyrrolidine (27.0 µL, 324 µmol, 10 mol%) in CH_2Cl_2 (13 mL) was heated to 45 °C and stirred for 1 h. The mixture was cooled to 0 °C, diluted with EtOAc (10 mL) and carefully quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were seperated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane/Et_2O, 4:1 to 1:2) to afford enal **SI-4** (456 mg, 2.74 mmol, 85%) as a colorless oil.

One-pot procedure from butenolide 7



A solution of butenolide **7** (190 mg, 1.05 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was cooled to –78 °C and a stream of ozone was passed through until a blue colour persisted. The excess ozone was then removed by saturating the solution with oxygen until the blue colour faded and triphenylphosphine (276 mg, 1.05 mmol, 1.0 equiv) was added. The cooling bath was removed and the reaction mixture was warmed to ambient temperature. Then aqueous formaldehyde solution (37 wt%, 118 µL, 1.58 mmol, 1.5 equiv), propionic acid (8 µL, 105 µmmol, 10 mol%) and pyrrolidine (35 µL, 422 µmol, 40 mol%) were added and stirring was continued at 45 °C for 1 h. The mixture was cooled to 0 °C, diluted with EtOAc (5 mL) and carefully quenched with saturated aqueous $NaHCO_3$ (5 mL). The layers were seperated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by MPLC (dry-loaded onto Celite®, SiO_2, cyclohexane/EtOAc, 100:0 to 4:1 to 1:1) to afford enal **SI-4** (119 mg, 713 µmol, 68%) as a colorless oil.



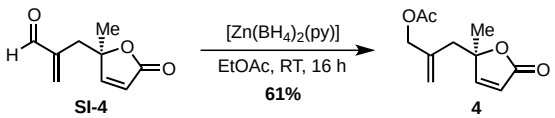
$[\alpha]_D^{20}$ = –4.4 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, H-8), 2.68 (d, *J* = 13.7 Hz, 1 H, H-5), 2.88 (d, *J* = 13.7 Hz, 1 H, H-5), 5.88 (d, *J* = 5.6 Hz, 1 H, H-2), 6.19 (s, 1 H, H-9), 6.49 (s, 1 H, H-9), 7.24 (d, *J* = 5.6 Hz, 1 H, H-3), 9.41 (s, 1 H, H-7) ppm.

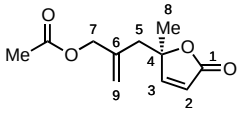
^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.5 (C-8), 35.4 (C-5), 87.3 (C-4), 120.9 (C-2), 140.2 (C-9), 143.0 (C-6), 159.5 (C-3), 172.3 (C-1), 194.2 (C-7) ppm.

HRMS (ESI, pos.): *m/z* calcd for $C_9H_{10}O_3Na^+$ [M+Na$^+$]: 189.0522, found 189.0526.

2.6 (5*R*)-5-Methyl-5-(3-(acetyloxy)-2-methyleneprop-1-yl)-3-oxolen-2-one (4)



Allyl acetate **4** was prepared in analogy to a reported procedure by ZEYNIZADEH and SETAMDIDEH for the reductive acetylation of carbonyl compounds.[11] To a solution of enal **SI-4** (270 mg, 1.63 mmol, 1.0 equiv) in anhydrous EtOAc (4.6 mL) at 0 °C was added zinc borohydride pyridine complex (297 mg, 1.71 mmol, 1.05 equiv). The resulting reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction was carefully quenched with saturated aqueous NH_4Cl (5 mL). The layers were seperated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O, 2:1 to 1:2) afforded allyl acetate **4** (209 mg, 994 µmol, 61%) as a colorless oil.



$[\alpha]_D^{20}$ = –10.2 (*c* = 1.00, $CHCl_3$).

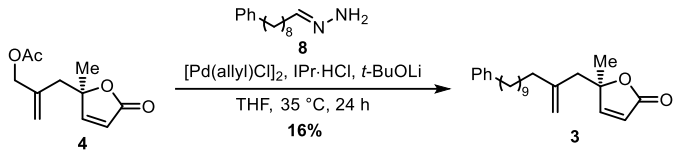
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 3 H, H-8), 2.09 (s, 3 H, Ac), 2.45 (d, *J* = 14.3 Hz, 1 H, H-5), 2.59 (d, *J* = 14.3 Hz, 1 H, H-5), 4.49 (s, 2 H, H-7), 5.05 – 5.07 (m, 1 H, H-9), 5.24 – 5.25 (m, 1 H, H-9), 6.03 (d, *J* = 5.6 Hz, 1 H, H-2), 7.38 (d, *J* = 5.6 Hz, 1 H, H-3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.0 (Ac), 24.1 (C-8), 41.9 (C-5), 66.9 (C-7), 88.0 (C-4), 118.9 (C-9), 121.2 (C-2), 137.6 (C-6), 159.7 (C-3), 170.7 (Ac), 172.2 (C-1) ppm.

HRMS (ESI, pos.): *m/z* calcd for $C_{11}H_{14}O_4Na^+$ [M+Na$^+$]: 233.0784, found 233.0787; calcd for $C_{11}H_{14}O_4K^+$ [M+K$^+$]: 249.0524, found 249.0530.

2.7 (5*R*)-5-Methyl-5-(12-phenyl-2-methylenedodec-1-yl)-3-oxolen-2-one (3)

Palladium-catalyzed allylic substitution with hydrazone 8

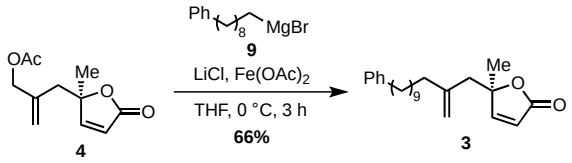


The following procedure was done in analogy to a reported protocol by LI et al. for the palladium-catalyzed alkylation of allyl acetates with hydrazones.[12]

Preparation of the hydrazone **8**: A mixture of 9-phenylnonanal (324 mg, 1.48 mmol, 1.0 equiv), hydrazine monohydrate (86.5 µL, 1.79 mmol, 1.2 equiv) and anhydrous Na_2SO_4 (120 mg) in THF (1.2 mL) was stirred at ambient temperature for 2 h. Then 5 Å molecular sieves powder (150 mg) was added and the solution was dried over night.

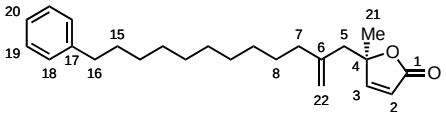
A flame-dried Schlenk tube was charged with 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10.0 mg, 24.0 µmol, 10 mol%) and allylpalladium(II) chloride dimer (4.40 mg, 12.0 µmol, 5 mol%) under an argon atmosphere. A solution of *t*-BuOLi (1 M in THF, 48.0 µL, 48.0 µmol, 20 mol%) was added and the mixture was stirred at ambient temperature for 1 h. Then a solution of allyl acetate **4** (50.0 mg, 238 µmol, 1.0 equiv) in THF (0.71 mL) was added and the mixture stirred for another 30 min before a solution of hydrazone **8** (1.25 M in THF, 0.24 mL, 300 µmol, 1.26 equiv) and *t*-BuOLi (1 M in THF, 480 µL, 480 µmol, 2.0 equiv) were added. The reaction mixture was stirred at 35 °C for 24 h and then filtered through a short pad of Celite®, rinsing with CH_2Cl_2 (3 × 5 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc, 8:1 to 6:1) to afford alkene **3** (13.8 mg, 389 µmol, 16%) as a colorless oil.

Iron-catalyzed allylic substitution with Grignard reagent 9



Preparation of the Grignard reagent (9-phenylnonylmagnesium bromide (**9**)): To a flame-dried Schlenk flask was added freshly ground magnesium (146 mg, 6.00 mmol, 1.5 equiv) and the flask was once more dried by heating with a heat gun under high vacuum while vigorously stirring the magnesium. After cooling to ambient temperature the vessel was placed under an argon atmosphere and a solution of (9-bromononyl)benzene (1.13 g, 4.00 mmol, 1.0 equiv) in anhydrous THF (3 mL) was slowly added over a period of 1 h. Stirring was continued for 16 h and then stopped. After the solids settled down, the clear solution was transferred with a syringe into another flame-dried Schlenk flask and stored under an argon atmosphere. The concentration was determined by titration with menthol in the presence of phenanthroline.[13]

Alkene **3** was prepared in analogy to a procedure by JACOBI VON WANGELIN et al. for the iron-catalyzed alkylation of allyl acetates with alkylmagnesium compounds.[14] A Schlenk tube was charged with anhydrous $Fe(OAc)_2$ (4.9 mg, 28 µmol, 10 mol%) and anhydrous LiCl (16.6 mg, 392 µmol, 1.4 equiv) and flame-dried under high vacuum until bubbling ceased. Then a solution of allyl acetate **4** (58.8 mg, 280 µmol, 1.0 equiv) in THF (1.3 mL) was added and the resulting mixture was cooled to 0 °C. The Grignard reagent **9** (0.9 M, 0.44 mL, 1.4 equiv) was added dropwise over a period of 2 h and stirring was continued for further 1 h at 0 °C. The reaction was quenched by the addition of 1 M HCl (2 mL) and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by MPLC (dry-loaded onto Celite®, SiO_2, cyclohexane/EtOAc, 100:1 to 10:1 to 6:1) to afford alkene **3** (65.4 mg, 185 µmol, 66%) as a colorless oil.



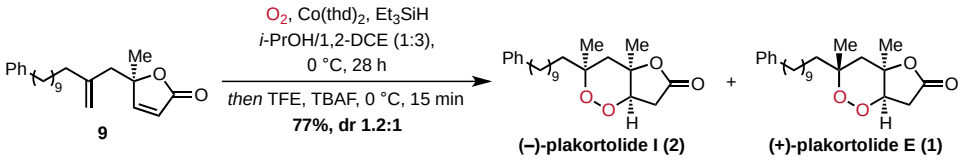
$[\alpha]_D^{24}$ = –12.3 (*c* = 1.00, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.21 – 1.36 (m, 12 H, CH_2), 1.36 – 1.42 (m, 2 H, H-9), 1.46 (s, 3 H, H-21), 1.59 – 1.64 (m, 2 H, H-15), 2.00 (t, *J* = 7.7 Hz, 2 H, H-7), 2.40 (d, *J* = 13.9 Hz, 1 H, H-5), 2.52 (d, *J* = 13.9 Hz, 1 H, H-5), 2.60 (t, *J* = 7.7 Hz, 2 H, H-16), 4.79 – 4.81 (m, 1 H, H-22), 4.93 – 4.94 (m, 1 H, H-22), 5.99 (d, *J* = 5.6 Hz, 1 H, H-2), 7.15 – 7.19 (m, 3 H, H-18, H-20), 7.26 – 7.29 (m, 2 H, H-19), 7.35 (d, *J* = 5.6 Hz, 1 H, H-3) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.1 (C-21), 27.9 (C-8), 29.35 (CH_2), 29.44 (CH_2), 29.61 (CH_2), 29.62 (CH_2), 29.66 (CH_2), 29.69 (CH_2), 31.6 (C-15), 36.1 (C-16), 37.0 (C-7), 44.9 (C-5), 88.7 (C-4), 115.4 (C-22), 120.6 (C-2), 125.7 (C-20), 128.3 (C-19), 128.5 (C-18), 143.1 (C-17), 143.6 (C-6), 160.4 (C-3), 172.5 (C-1) ppm.

HRMS (ESI, pos.): *m*/*z* calcd for $C_{24}H_{34}O_2Na^+$ [M+Na$^+$]: 377.2451, found 377.2465.

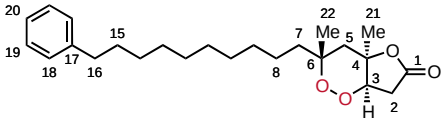
2.8 (3*R*,4a*R*,7a*R*)-3,4a-dimethyl-6-oxo-3-(10-phenyldec-1-yl)oxolano[3,2-*c*]-1,2-dioxane (1) and (3*S*,4a*R*,7a*R*)-3,4a-dimethyl-6-oxo-3-(10-phenyldec-1-yl)oxolano[3,2-*c*]-1,2-dioxane (2)



A flame-dried Schlenk flask was charged with bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt(II) (53.3 mg, 125 µmol, 30 mol%), 1,2-dichloroethane (6 mL) and half the amount of Et_3SiH (80.0 µL, 501 µmol, 1.2 equiv). The solution was saturated with a stream of oxygen for 5 min and stirred for 1 h under an atmosphere of oxygen. Then **4** (148 mg, 417 µmol, 1.0 equiv) and *i*-PrOH (2 mL) were added at

0 °C, followed by the dropwise addition of the remaining half of Et_3SiH (80.0 µL, 501 µmol, 1.2 equiv) in 1,2-dichloroethane (0.05 mL) over 3 h. After stirring for 28 h the reaction mixture was cooled to –5 °C and TFE (300 µL, 4.18 mmol, 10.0 equiv) and TBAF (1 M, 1.00 mL, 2.4 equiv) were added. The mixture was warmed to 0 °C and stirred for 15 min and then diluted with H_2O (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, pentane/CH_2Cl_2, 1:3) to give **1** (57.0 mg, 147 µmol, 35%) as a colorless solid and **2** (68.4 mg, 176 µmol, 42%) as a colorless oil.

(+)-Plakortolide E (1)



$[\alpha]_D^{24}$ = +10.1 (*c* = 1.00, $CHCl_3$); Lit.[15]: $[\alpha]_D$ = +8.0 (*c* = 0.0173, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.24 – 1.38 (m, 14H, CH_2), 1.29 (s, 2H, H-22), 1.38 (s, 3H, H-21), 1.46 – 1.51 (m, 1H, H-7), 1.51 – 1.58 (m, 1H, H-7), 1.59 – 1.64 (m, 2H, H-15), 1.71 (d, *J* = 14.8 Hz, 1H, H-5), 2.17 (d, *J* = 14.8 Hz, 1H, H-5), 2.58 – 2.65 (m, 3H, H-2, H-16), 2.91 (dd, *J* = 18.5, 6.2 Hz, 1H, H-2), 4.45 (d, *J* = 6.2 Hz, 1H, H-3), 7.16 – 7.19 (m, 3H, H-18, H-20), 7.26 – 7.29 (m, 2H, H-19) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 22.5 (C-22), 23.2 (CH_2), 26.0 (C-21), 29.4 (CH_2), 29.59 (2C, CH_2), 29.63 (2C, CH_2), 30.1 (CH_2), 31.6 (C-15), 34.4 (C-2), 36.1 (C-16), 40.7 (C-5), 41.1 (C-7), 80.2 (C-6), 81.2 (C-3), 82.9 (C-4), 125.7 (C-20), 128.3 (2C, C-19), 128.5 (2C, C-18), 143.0 (C-17), 174.4 (C-1) ppm.

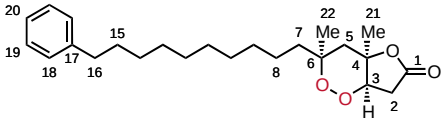
HRMS (ESI, pos.): *m*/*z* calcd for $C_{24}H_{36}O_4Na^+$ [M+Na$^+$]: 411.2506, found 411.2522.

m. p.: 54 – 55 °C.

X-ray: Crystals were grown by slow evaporation of a solution of **1** in pentane and Et_2O in a 1 mL vial at ambient temperature.

The spectroscopic data is in accordance with the literature.[15]

(–)-Plakortolide I (2)



$[\alpha]_D^{24}$ = –5.8 (*c* = 1.00, $CHCl_3$); Lit.[16]: $[\alpha]_D^{20}$ = –8 (*c* = 0.05, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.20 (s, 3H, H-22), 1.24 – 1.36 (m, 14H, CH_2), 1.37 (s, 3H, H-21), 1.52 – 1.58 (m, 1H, H-7), 1.58 – 1.64 (m, 2H, H-15), 1.65 (d, *J* = 15.0 Hz, 1H, H-5), 1.70 – 1.77 (m, 1H, H-7), 2.27 (d, *J* = 15.0 Hz, 1H, H-5), 2.56 (d, *J* = 18.5 Hz, 1H, H-2), 2.60 (t, *J* = 7.8 Hz, 2H, H-16), 2.90 (dd, *J* = 18.5, 6.0 Hz, 1H, H-2), 4.47 (d, *J* = 6.0 Hz, 1H, H-3), 7.15 – 7.25 (m, 3H, H-18, H-20), 7.25 – 7.29 (m, 2H, H-19) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 23.8 (CH_2), 25.0 (C-22), 26.0 (C-21), 29.4 (CH_2), 29.59 (CH_2) 29.64 (2C, CH_2), 29.7 (CH_2), 30.1 (CH_2), 31.6 (C-15), 34.2 (C-2), 36.1 (C-16), 37.0 (C-7), 40.3 (C-5), 80.3 (C-6), 80.9 (C-3), 82.6 (C-4), 125.6 (C-20), 128.3 (C-19), 128.5 (C-18), 143.1 (C-17), 174.2 (C-1) ppm.

HRMS (ESI, pos.): *m*/*z* calcd for $C_{24}H_{36}O_4Na^+$ [M+Na$^+$]: 411.2506, found 411.2524.

The spectroscopic data is in accordance with the literature.[16]

3. X-ray data

(+)-Plakortolide E (1) (CCDC2074855)

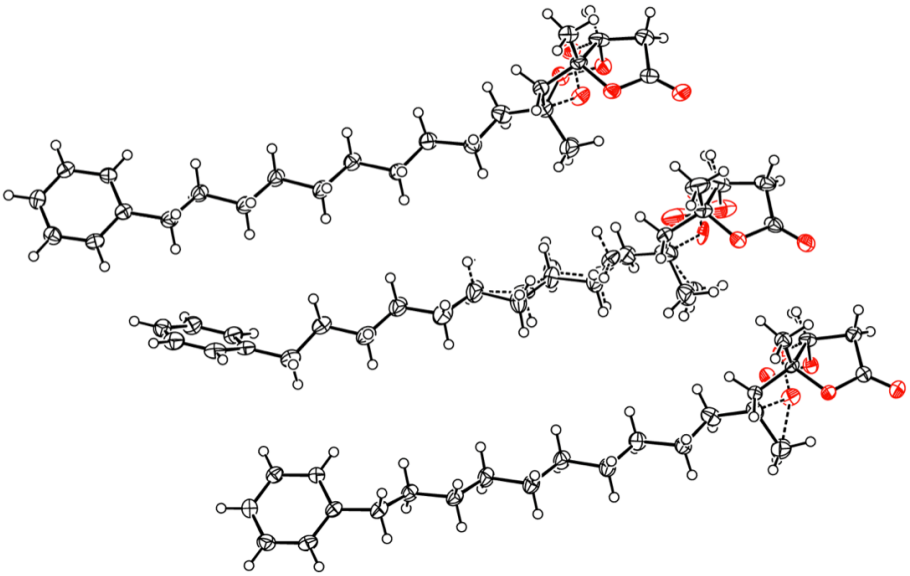
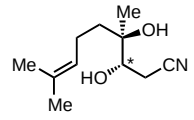


Table S1. Crystal data of (+)-plakortolide E (1).

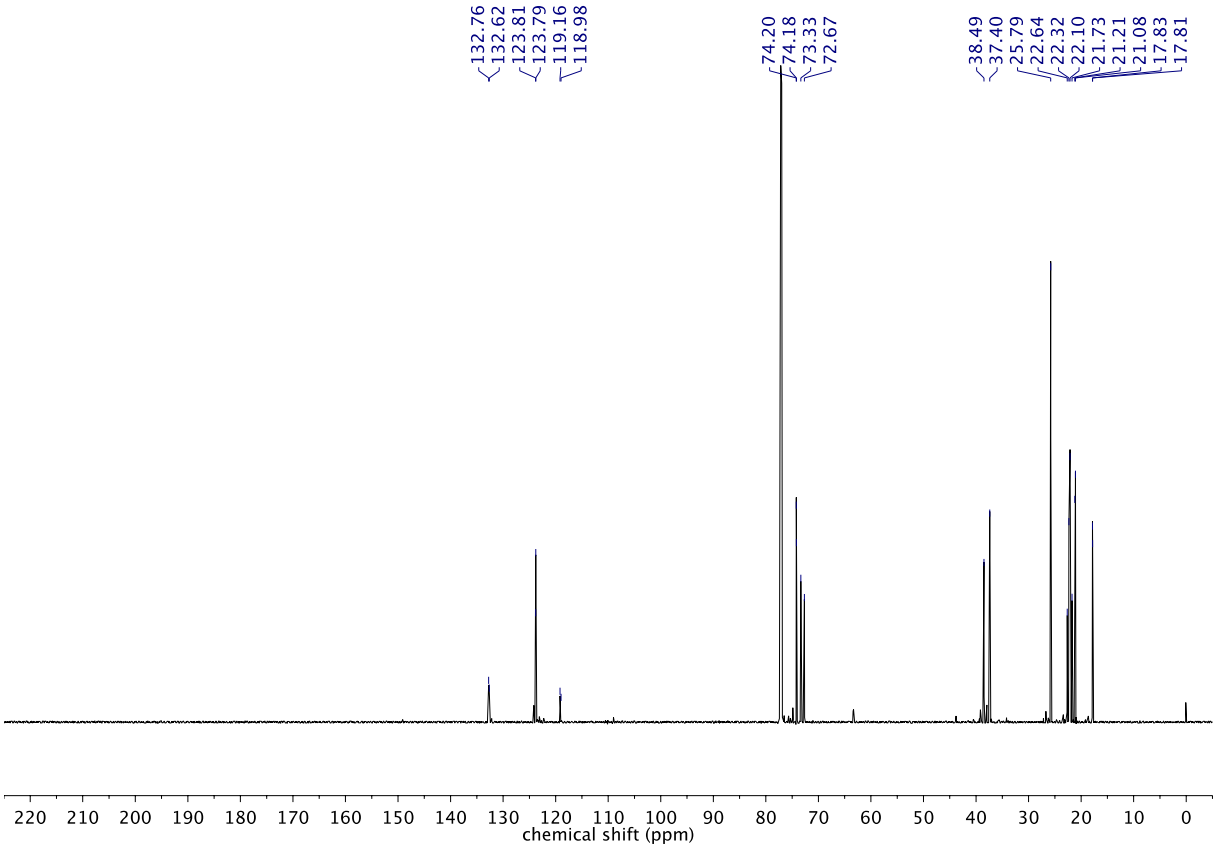
Empirical formula	$C_{72}H_{108}O_{12}$
Formula weight	1165.58
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.7306(2)
b/Å	17.1506(7)
c/Å	34.0117(14)
α/°	90
β/°	93.473(2)
γ/°	90
Volume/Å^3	3336.6(2)
Z	2
ρ_{calc}/gcm^{-3}	1.160
μ/mm^{-1}	0.611
F(000)	1272.0
Crystal size/mm^3	0.754 × 0.126 × 0.052
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	5.206 to 136.548
Reflections collected	129589
Independent reflections	12052 [R_{int} = 0.0410, R_{sigma} = 0.0174]
Data/restraints/parameters	12052/6/860
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0380, wR_2 = 0.0906
Final R indexes [all data]	R_1 = 0.0390, wR_2 = 0.0915
Largst diff. peak and hole/e.Å^{-3}	0.45 and –0.63
Flack parameter	0.02(2)
CCDC deposition number	2074855

4. NMR Spectra

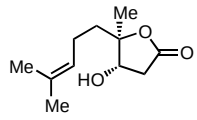
Nitrile 6

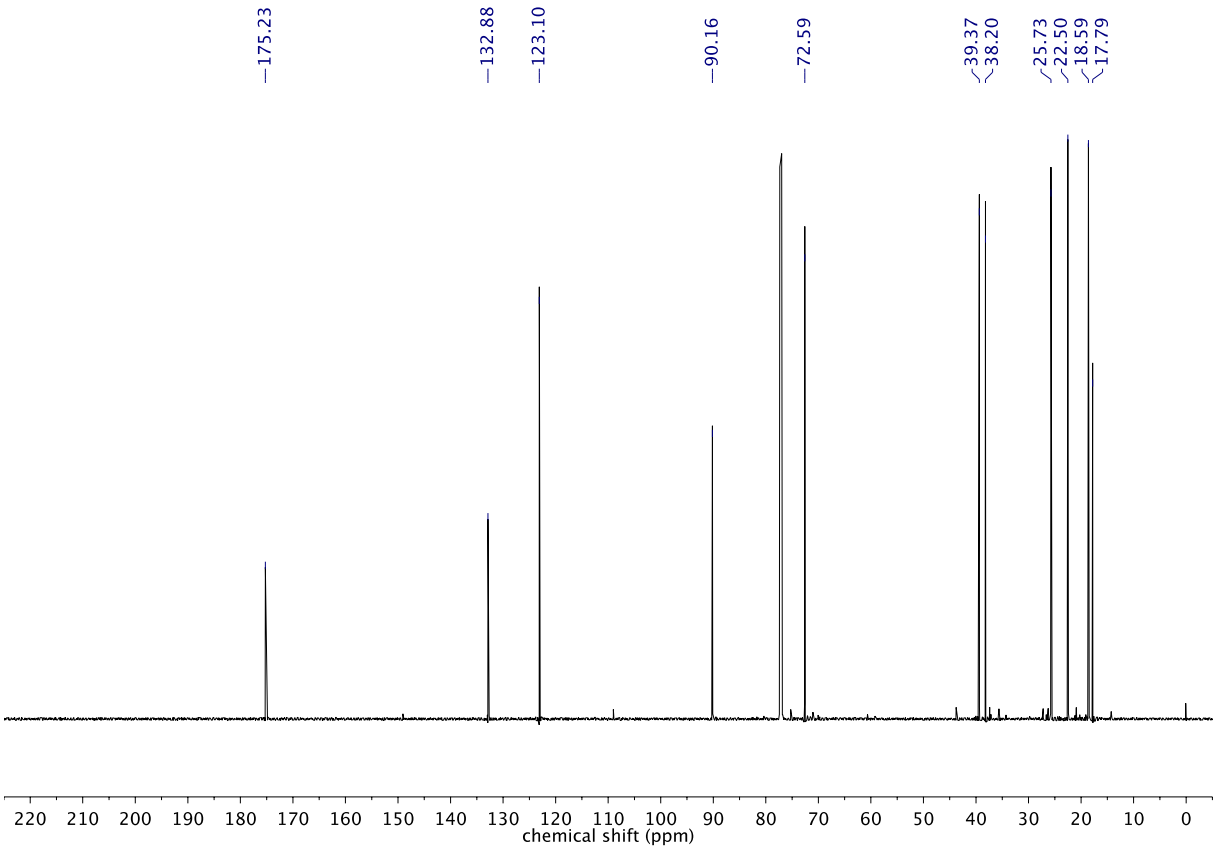


dr 3:2, *major indicated

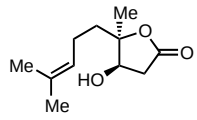


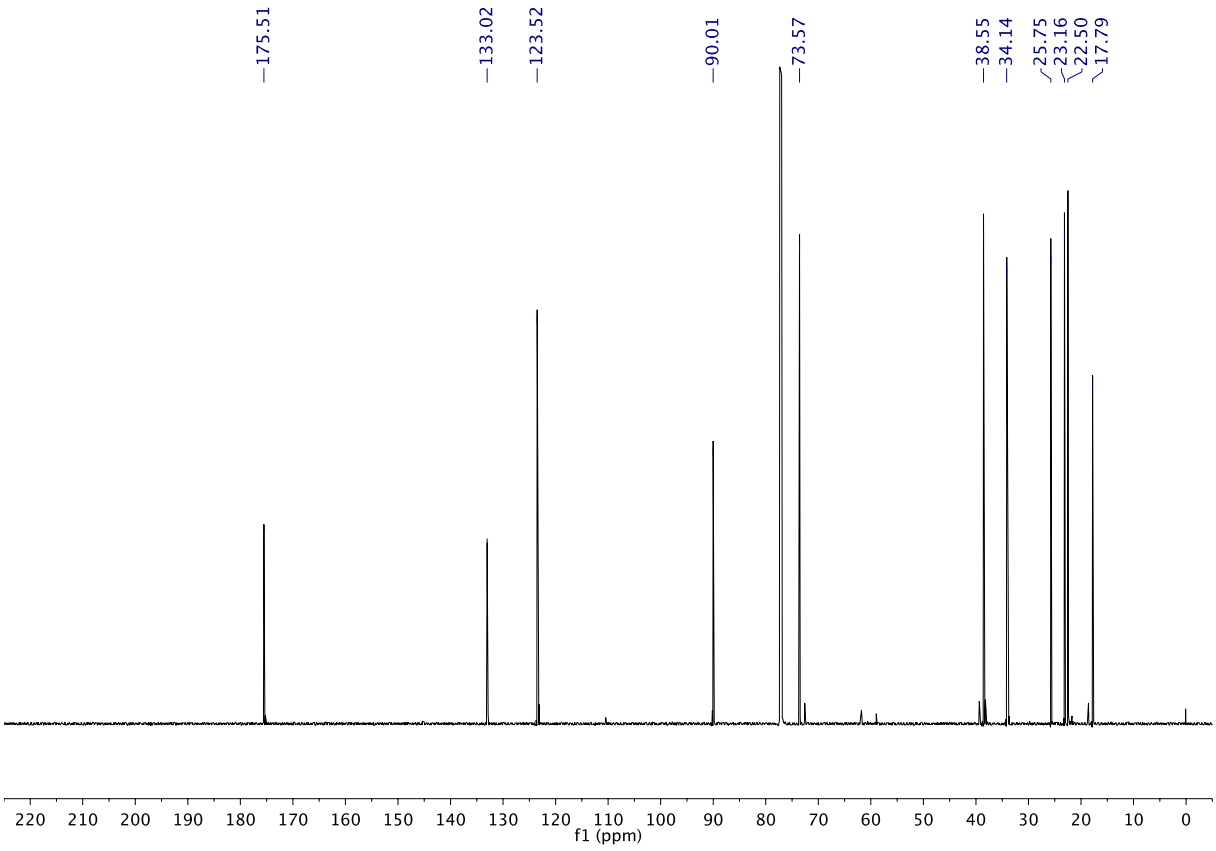
***trans*-Lactone SI-2**



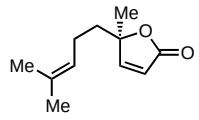


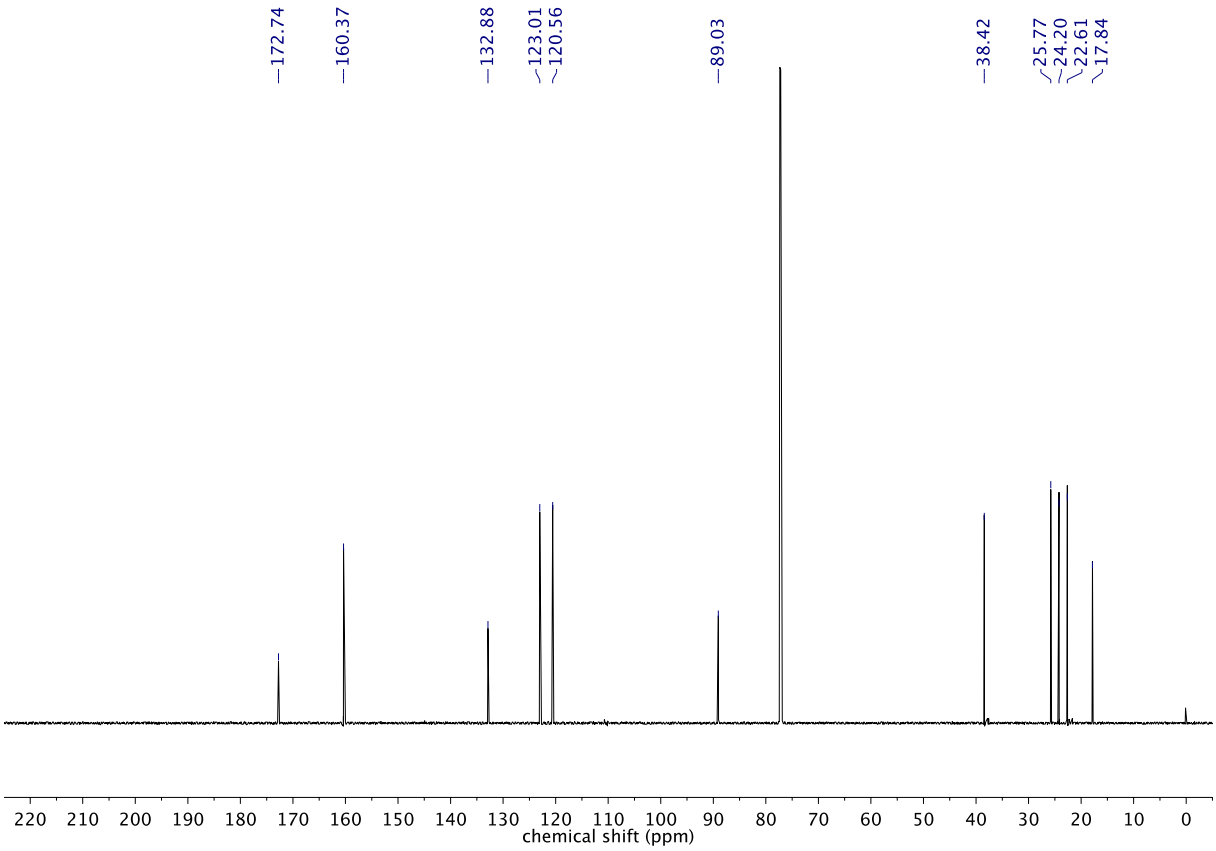
***cis*-Lactone SI-2**



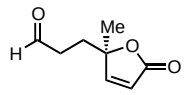


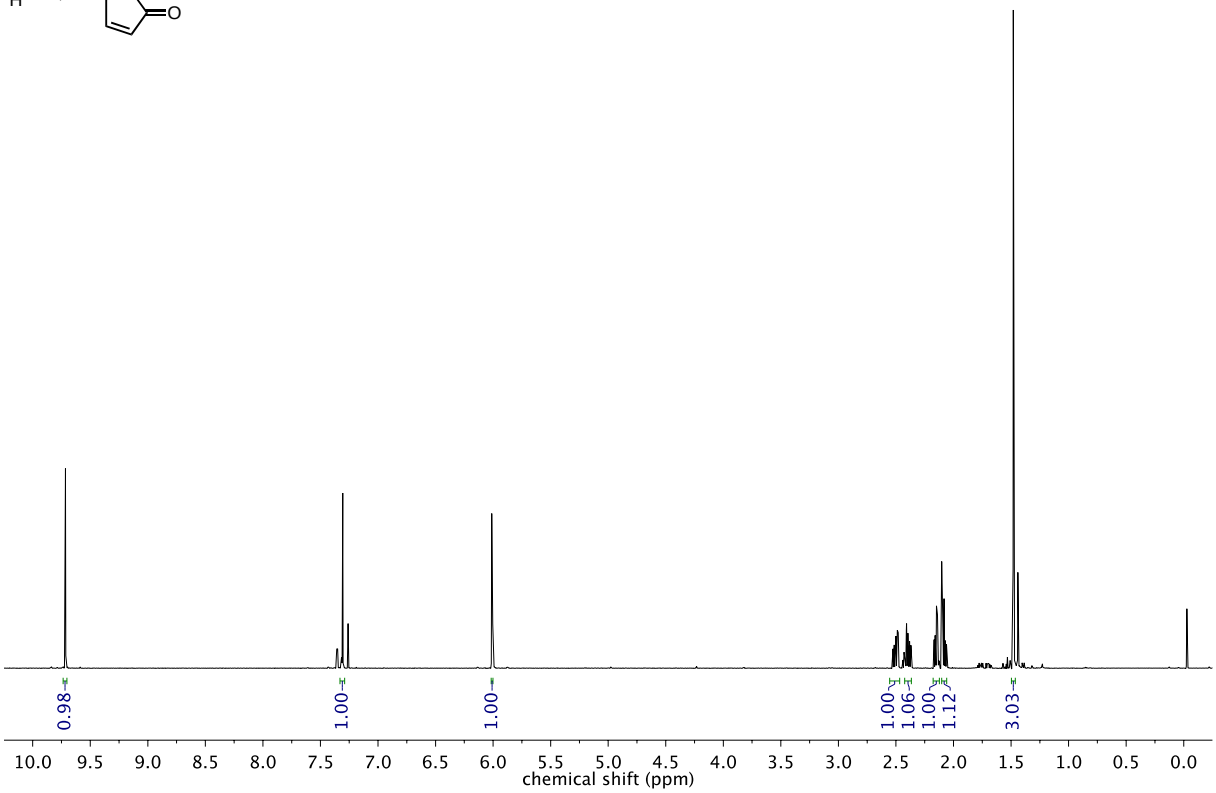
Butenolide 7

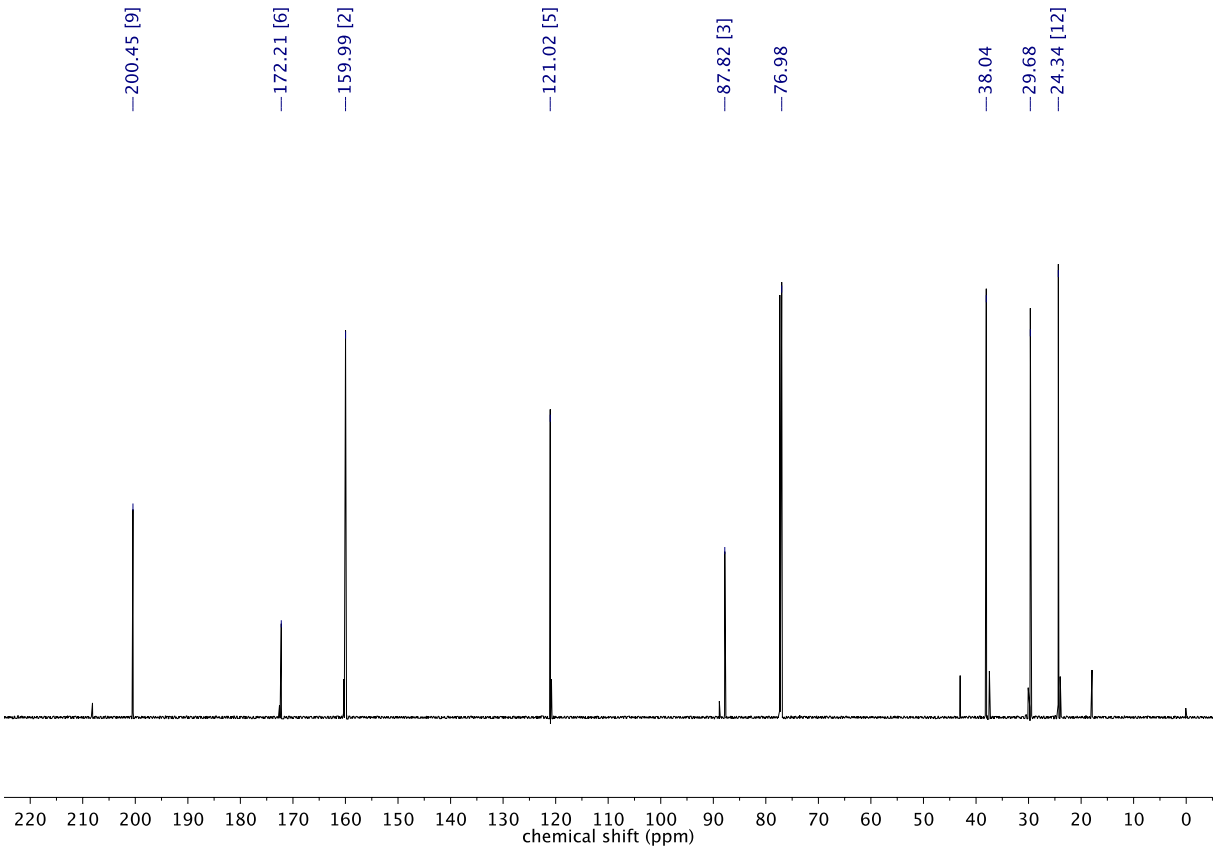




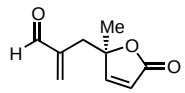
Aldehyde SI-3

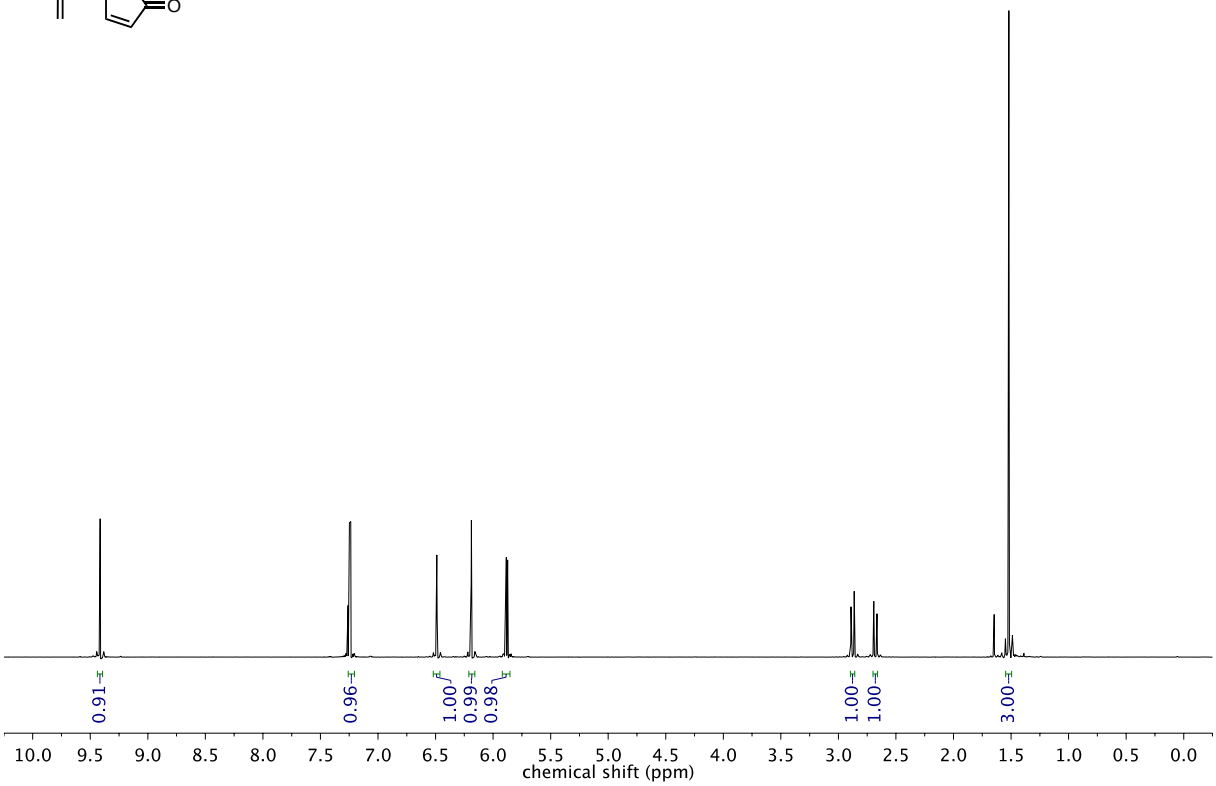


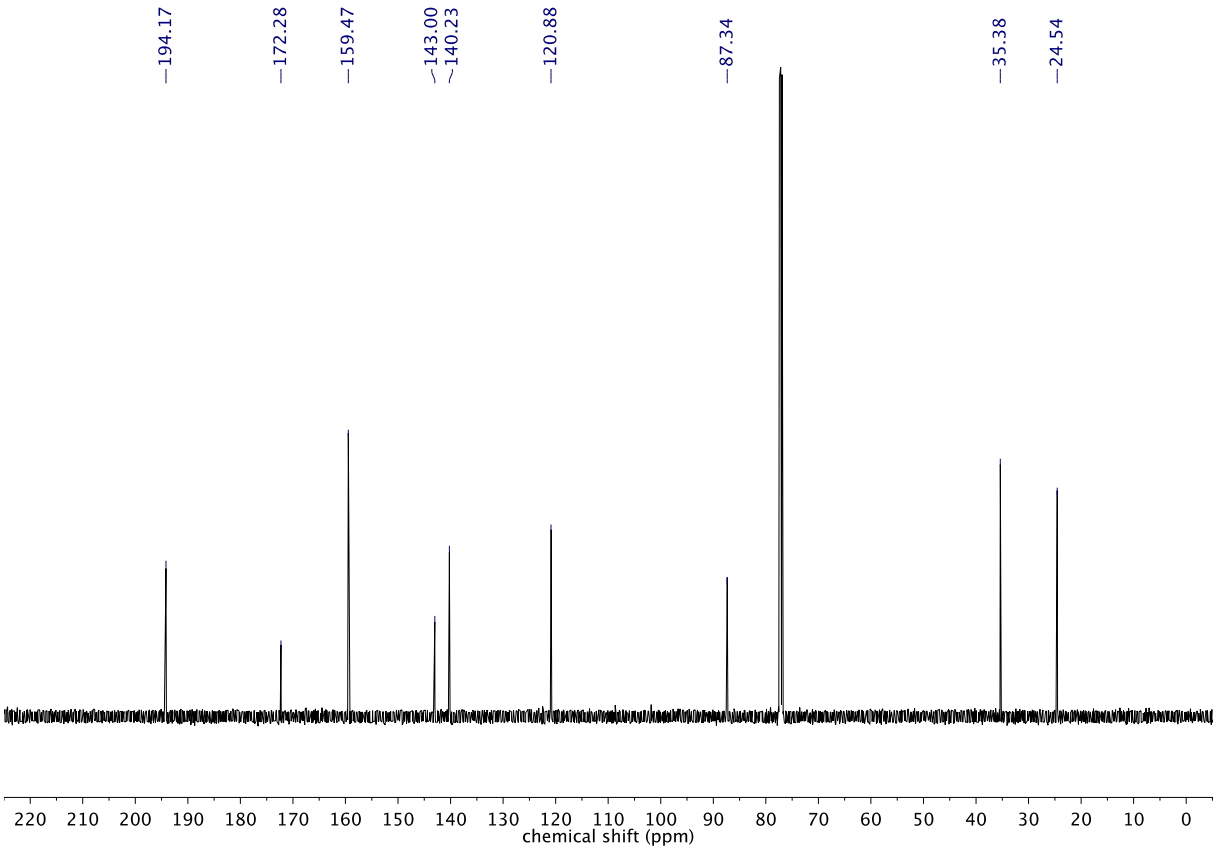




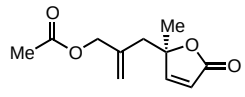
Enal SI-4

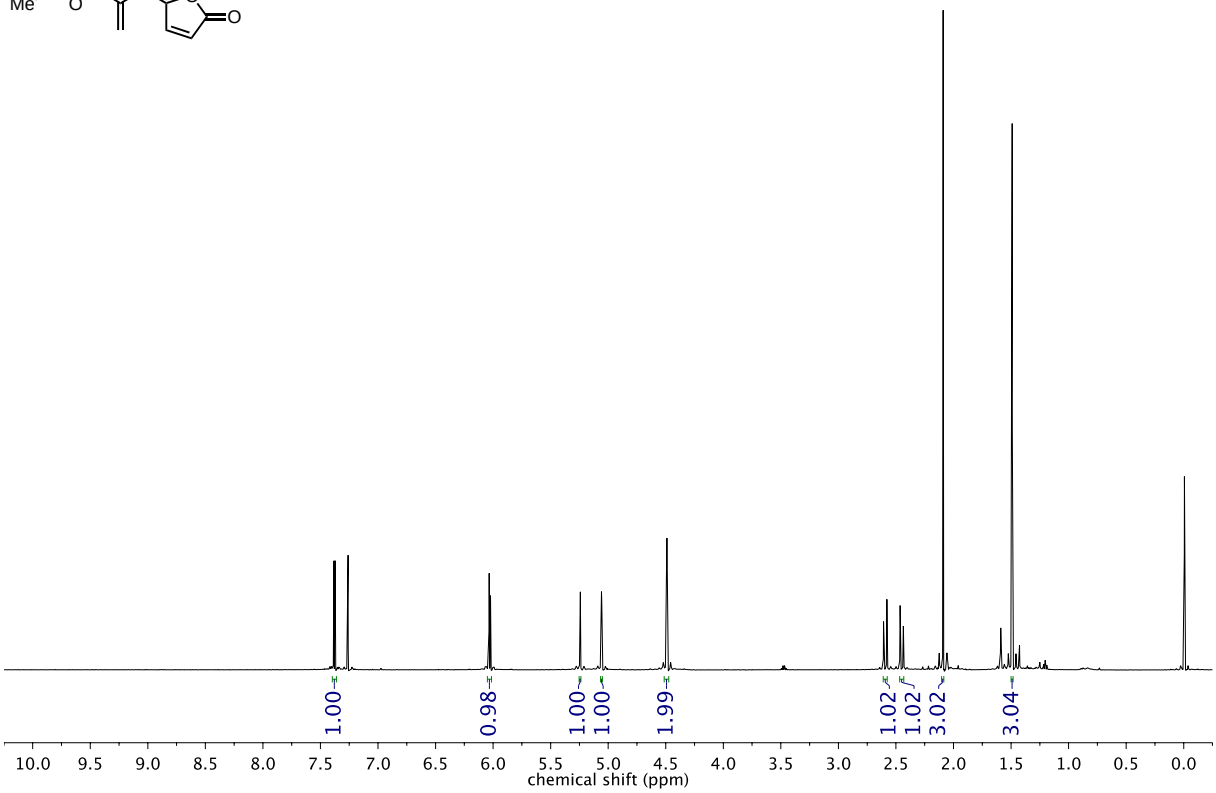

O
H
Me
O
O

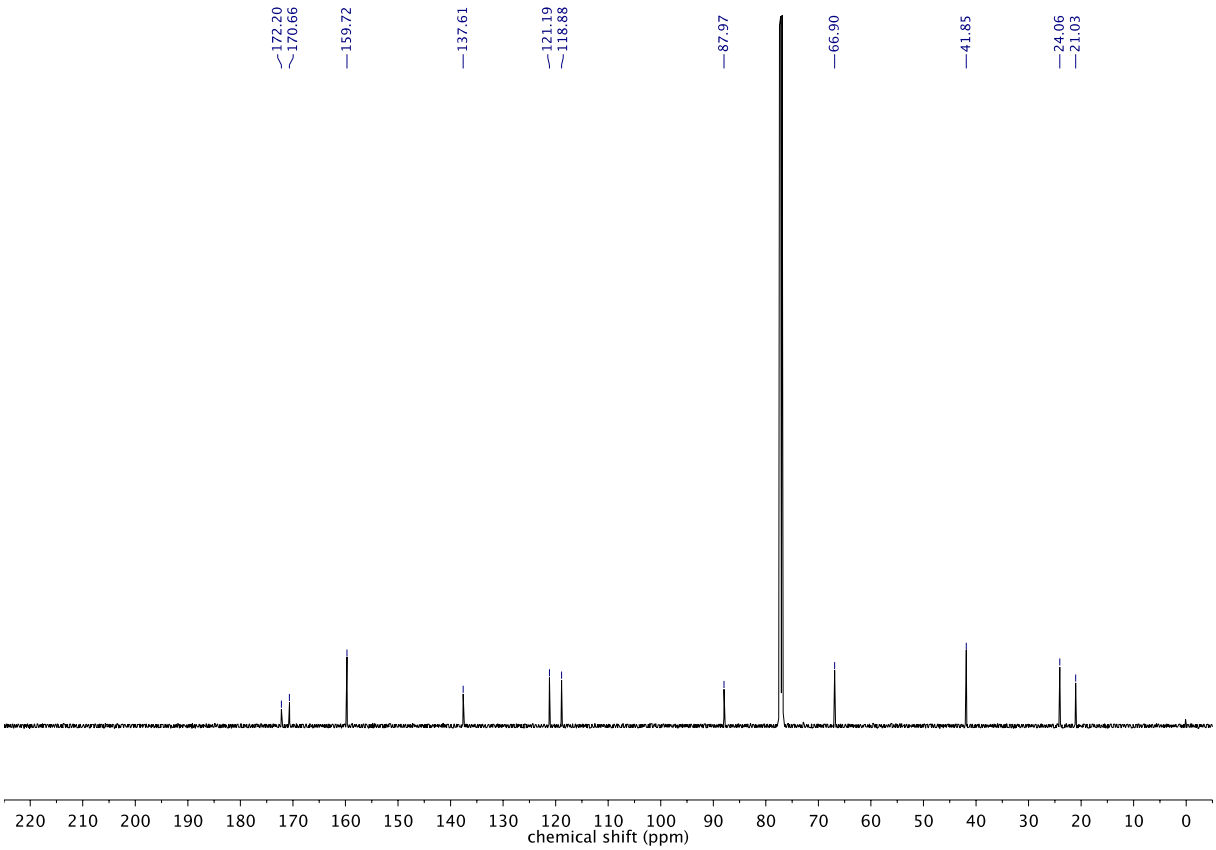

0.91
0.96
1.00
0.99
0.98
1.00
1.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
chemical shift (ppm)


194.17
172.28
159.47
143.00
140.23
120.88
87.34
35.38
24.54
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift (ppm)

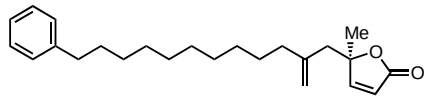
Allyl acetate 4

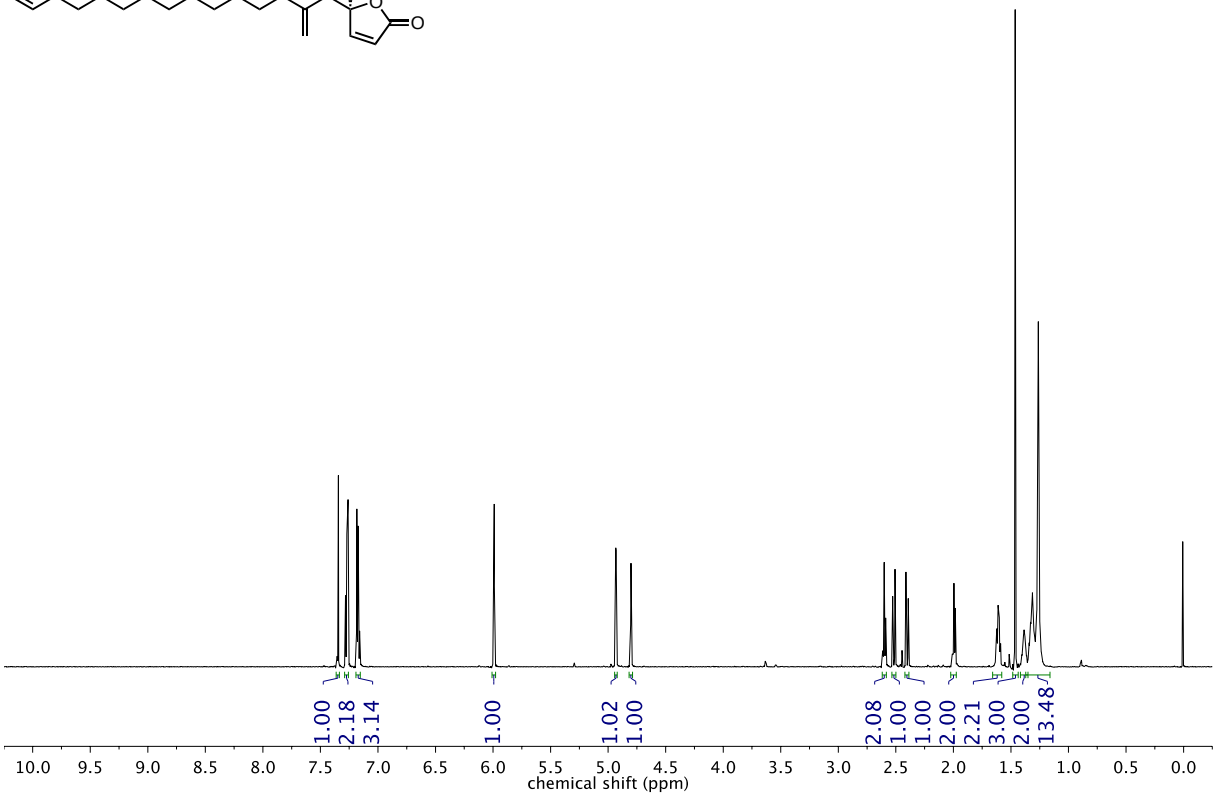


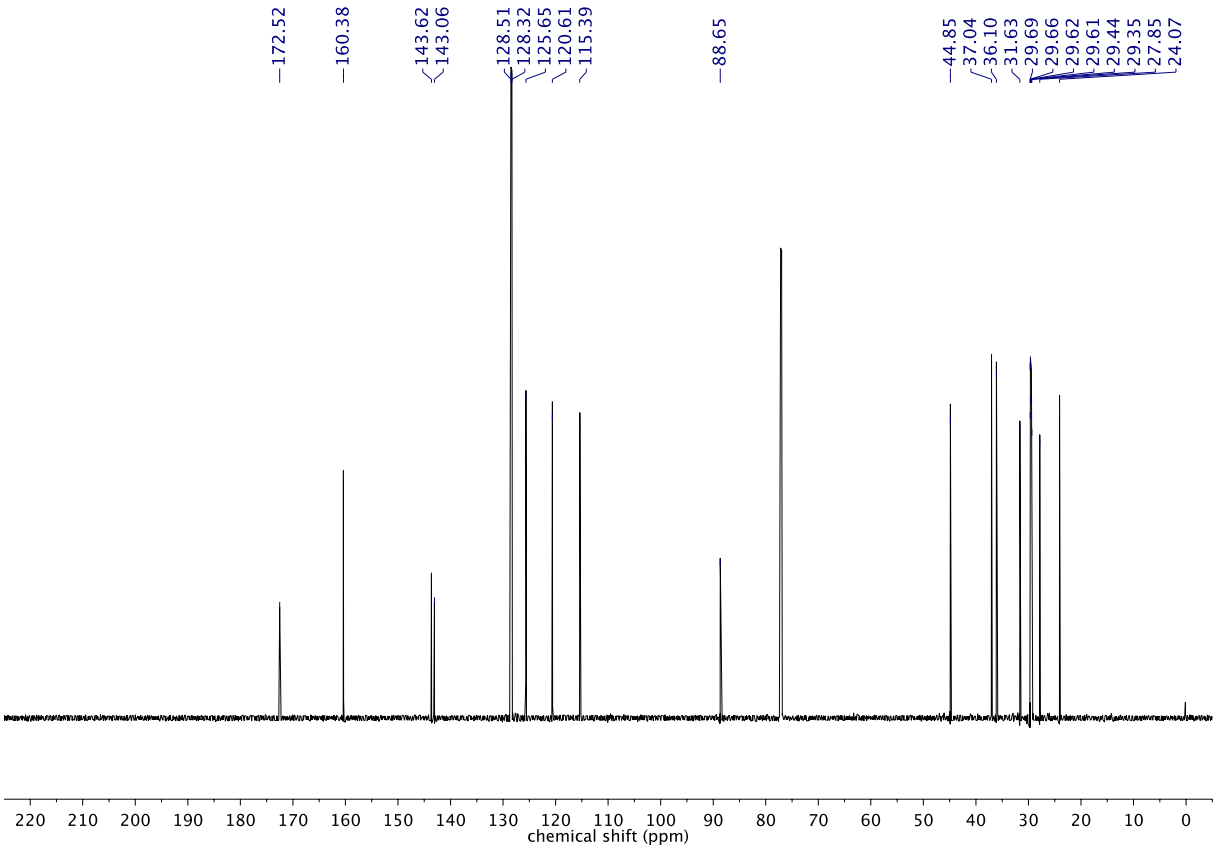




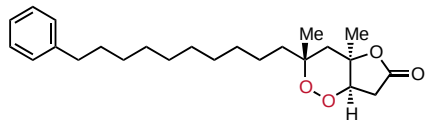
Alkene 3

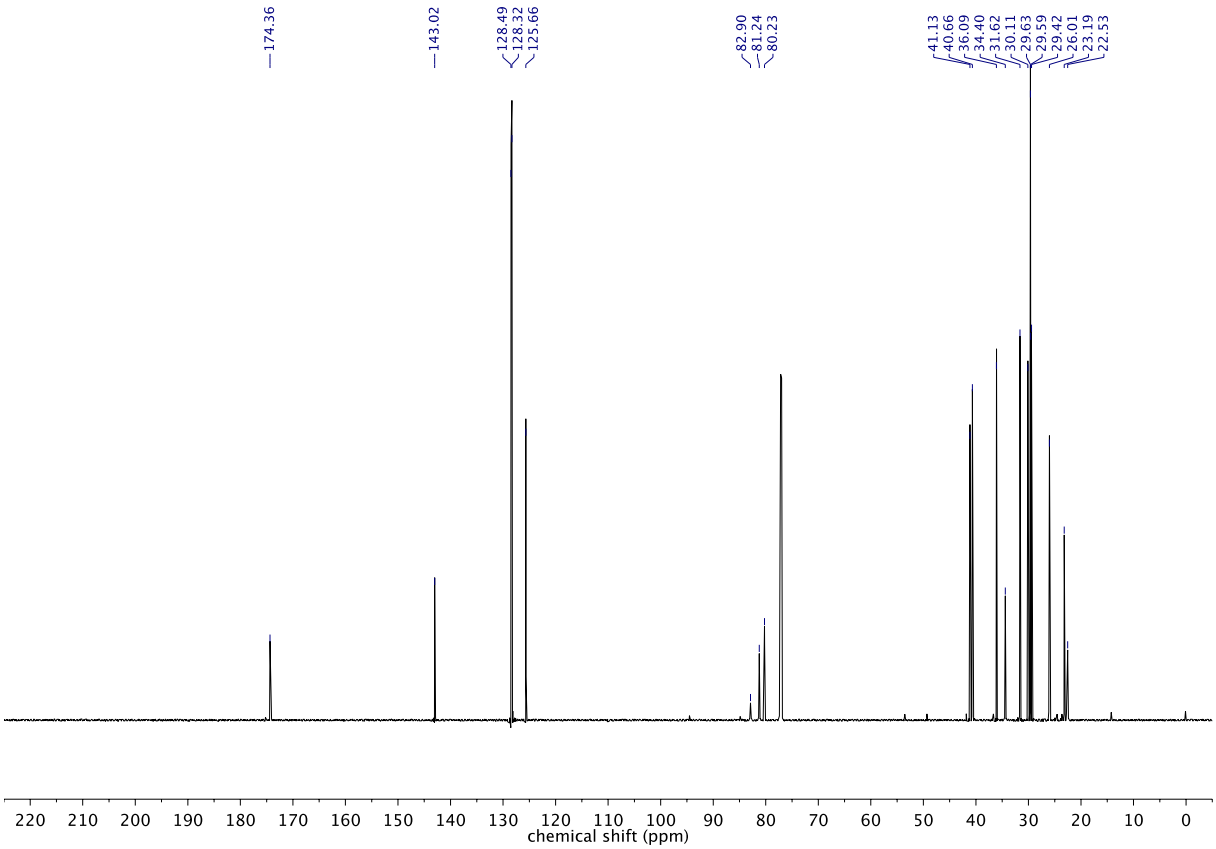

Me
O
O


1.00
2.18
3.14
1.00
1.02
1.00
2.08
1.00
1.00
2.00
2.21
3.00
2.00
13.48
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
chemical shift (ppm)

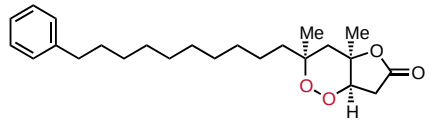

172.52
160.38
143.62
143.06
128.51
128.32
125.65
120.61
115.39
88.65
44.85
37.04
36.10
31.63
29.69
29.66
29.62
29.61
29.44
29.35
27.85
24.07
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
chemical shift (ppm)

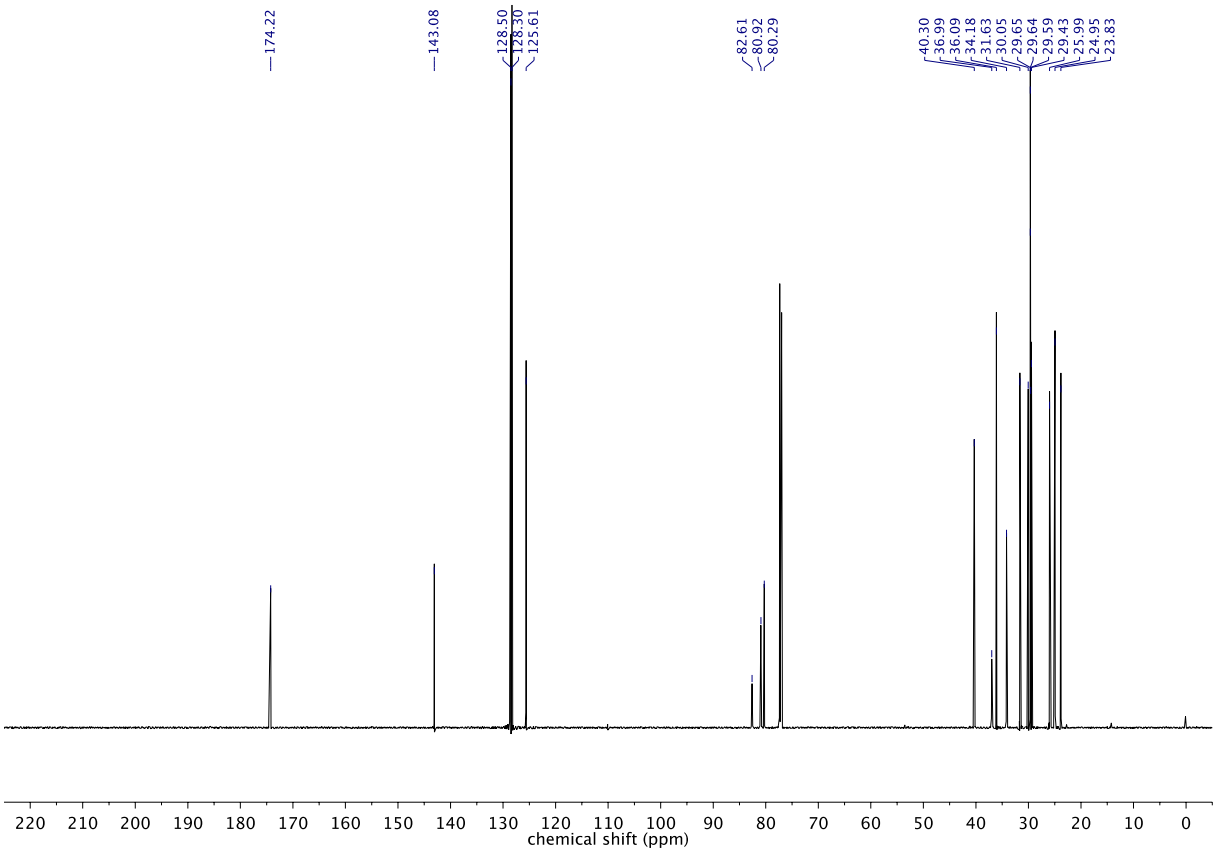
(+)-Plakortolide E (1)





(–)-Plakortolide I (2)





5. References

(1) Langhanki, J.; Rudolph, K.; Erkel, G.; Opatz, T. Total synthesis and biological evaluation of the natural product (−)-cyclonerodiol, a new inhibitor of IL-4 signaling. *Org. Biomol. Chem.* **2014**, *12*, 9707–9715.

(2) Zeynizadeh, B.; Zahmatkesh, K. First and Efficient Method for Reduction of Aliphatic and Aromatic Nitro Compounds with Zinc Borohydride as Pyridine Zinc Tetrahydroborato Complex: A New Stable Ligand-Metal Borohydride. *J. Chin. Chem. Soc.* **2003**, *50*, 267–271.

(3) Chen, X.; Cheng, Z.; Guo, J.; Lu, Z. Asymmetric remote C-H borylation of internal alkenes via alkene isomerization. *Nat. Commun.* **2018**, *9*, 3939.

(4) Barnych, B.; Vatèle, J.-M. Total Synthesis of *seco*-Plakortolide E and (–)-*ent*-Plakortolide I: Absolute Configurational Revision of Natural Plakortolide I. *Org. Lett.* **2012**, *14*, 564–567

(5) Sheldrick, G. M. A short history of *SHELX*. *Acta Cryst.* **2008**, *A64*, 112–122.

(6) Sheldrick, G. M. Crystal structure refinement with *SHELX*. *Acta Cryst.* **2015**, *C71*, 3–8.

(7) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *OLEX2*: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341.

(8) Leisering, S.; Riaño, I.; Depken, C.; Gross, L. J.; Weber, M.; Lentz, D.; Zimmer, R.; Stark, C. B. W.; Breder, A.; Christmann, M. Synthesis of (+)-Greek Tobacco Lactone via a Diastereoablative Epoxidation and a Selenium-Catalyzed Oxidative Cyclization. *Org. Lett.* **2017**, *19*, 1478–1481.

(9) Siitonen, J. H.; Pihko, P. M. Total Synthesis of (+)-Greek Tobacco Lactone. *Synlett* **2014**, *25*, 1888–1890.

(10) Benohoud, M.; Erkkilä, A.; Pihko, P. M. ORGANOCATALYTIC α-METHYLENATION OF ALDEHYDES: PREPARATION OF 3,7-DIMETHYL-2-METHYLENE-6-OCTENAL. *Org. Synth.* **2010**, *87*, 201–208.

(11) Zeynizadeh, B.; Setamdideh, D.; Faraji, F. Reductive Acetylation of Carbonyl Compounds to Acetates with Pyridine Zinc Borohydride. *Bull. Korean Chem. Soc.* **2008**, *29*, 76–80.

(12) Zhu, D.; Lv, L.; Li, C.-C.; Ung, S.; Gaom, J.; Li, C.-J. Umpolung of Carbonyl Groups as Alkyl Organometallic Reagent Surrogates for Palladium-Catalyzed Allylic Alkylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 16520–16524.

(13) Lin, H.-S.; Paquette, L. A. A Convenient Method for Determining the Concentration of Grignard Reagents. *Synth. Commun.* **1994**, *24*, 2503–2506.

(14) Bernauer, J.; Wu, G.; Jacobi von Wangelin, A. Iron-catalysed allylation-hydrogenation sequence as masked alkyl-alkyl cross-couplings. *RSC Adv.* **2019**, *9*, 31217–31223.

(15) Rudi, A.; Afanii, R.; Gravalos, L. G.; Aknin, M.; Gaydou, E.; Vacelet, J.; Kashman, Y. Three New Cyclic Peroxides from the Marine Sponge *Plakortisaff simplex*. *J. Nat. Prod.* **2003**, *66*, 682–685.

(16) Qureshi, A.; Salvà, J.; Harper, M.; Faulkner, D. J. New Cyclic Peroxides from the Philippine Sponge *Plakinastrella* sp. *J. Nat. Prod.* **1998**, *61*, 1539–1542.