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Total Syntheses of Paraconic Acids and 1,10-*seco*-Guaianolides via a Barbier Allylation/Translactonization Cascade of 3-(Bromomethyl)-2(5*H*)-furanone

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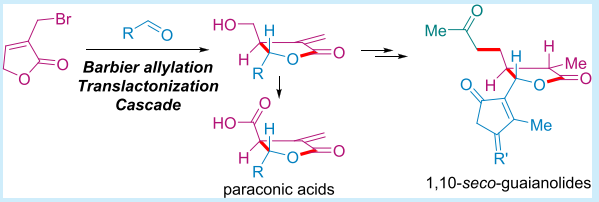
ABSTRACT: A palladium-catalyzed Barbier allylation/translactonization cascade reaction was established for the rapid construction of β,γ-disubstituted α-*exo*-methylene-γ-butyrolactone, an important motif in sesquiterpenes. Dimethyl zinc played significant roles in both steps for the umpolung of π-allylpalladium as a nucleophile and promoting a Lewis acid-mediated translactonization. This sequence showed a broad substrate scope and was further harnessed for the synthesis of two paraconic acids as well as the first protecting-group-free total synthesis of two 1,10-*seco*-guaianolides.



Sesquiterpene lactones are a rich source of bioactive natural products, and an α-*exo*-methylene-γ-butyrolactone moiety is often central to their biological activity.[1] Well-studied and recent examples include helenalin (**1**),[2] parthenolide (**2**),[3] arglabin (**3**),[4] deoxyelephantopin (**4**),[5] and tagitinin F (**5**)[6] (Figure 1a). This framework is also found in paraconic acids (**6**),[7] and the synthesis of α-*exo*-methylene-γ-butyrolactones has attracted significant interest over the years.[8] The biosynthetic pathways leading to sesquiterpene lactones intrinsically produce a combinatorial output of natural products; accordingly, different diastereomeric relationships in the butyrolactones are found across the family of natural products (Figure 1a).

The presence of a hydroxyl group two carbons away from the methylene unit of the γ-butyrolactone in many sesquiterpenes offers the opportunity for a strategic disconnection to an aldehyde (**8**) and an allylic bromide 3-(bromomethyl)-2(5*H*)-furanone (**7**, Figure 1b). This reaction is well-precedented using a variety of metals (Zn^0, In^0, Cr^{2+})[9] and affords the desired allylation product (**10**) in a good yield and diastereoisomeric purity based on a Zimmerman–Traxler transition state.[10] This methodology has been widely used in the total syntheses of butyrolactone antibiotics,[11] sesquiterpene lactones,[5,12] paraconic acids,[9] and lignans.[9,13] While this strategy reliably affords an *anti*-relationship between the substituents, examples of a *syn*-relationship (**9**) among the natural products beg for alternative methodologies. Our interest in the synthesis and biological investigation of sesquiterpene lactones[5,14] led us to revisit a report of a palladium-catalyzed diastereoselective allylation using dimethyl zinc as a stoichiometric reducing agent to afford a *syn*-configuration.[15] We found that the transformation with 1 equiv, or a slight excess, of dimethyl zinc afforded the *trans*-configuration, and the use of an excess of dimethyl zinc promoted a further translactonization to give **11** (Figure 1c).

We initiated our work using hexanal (**8a**) and bromolactone **7**, a reported substrate pair for the palladium-catalyzed reaction,[15] and compared the results of this reaction with the results of the $CrCl_2$-mediated allylation, which affords the *trans*-configuration (**10a**, Scheme 1). Indeed, the products were spectroscopically different. However, performing the palladium-catalyzed reaction under the same conditions but with 1.2 equiv of dimethyl zinc afforded the same product as that obtained with the $CrCl_2$-mediated allylation (**10a**). Puzzled by these results, we next treated the *trans*-configuration product (**10a**) obtained in the $CrCl_2$-mediated allylation with dimethyl zinc and observed a clean conversion to the same product as that obtained in the palladium-catalyzed reaction with an excess of dimethyl zinc (**11a**). Collectively, these results suggest that the palladium-catalyzed reaction yields the *trans*-configuration, likely proceeding through a Zimmerman–Taxler transition state (Scheme 1, **I**) as with other metals. However, the excess of dimethyl zinc used for the umpolung of π-allylpalladium as a nucleophile[15] can promote a Lewis acid-mediated translactonization. The complexation of a Lewis acid to the secondary alcohol and carbonyl results in unfavorable steric

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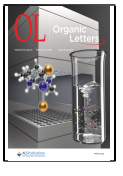

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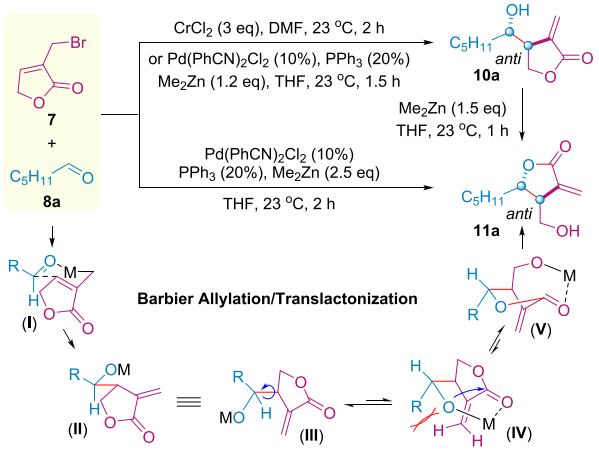
Scheme 1. Formation of *β,γ*-Disubstituted *α-exo*-Methylene-*γ*-butyrolactone with an *anti*-Configuration via a Barbier Allylation/Translactonization Sequence



interactions (Scheme 1, **IV**), which are relieved upon translactonization and drive the equilibrium to product **11a**.

We next investigated the scope of the palladium-catalyzed allylation and translactonization sequence (Scheme 2). Aliphatic aldehyde afforded the desired products (**11a–d**) across a range of examples (*α*-branched or linear, four examples) with good yields and selectivities (dr > 20:1 for all but **11a**). Aromatic aldehydes, including electron-poor and electron-rich substrates, were found to proceed with excellent diastereoselectivities (dr > 20:1) and in good yields (**11e–k**, seven examples 68–93%). Interestingly, unsaturated aldehydes were found to participate in the allylation reaction but not in the translactonization despite attempts to drive the rearrangement with an even larger excess of dimethyl zinc (up to 5 equiv, three examples, **10l–n**). A possible explanation is the lower steric demand of the sp^2 carbon relative to that of an sp^3 carbon, albeit the aromatic aldehyde

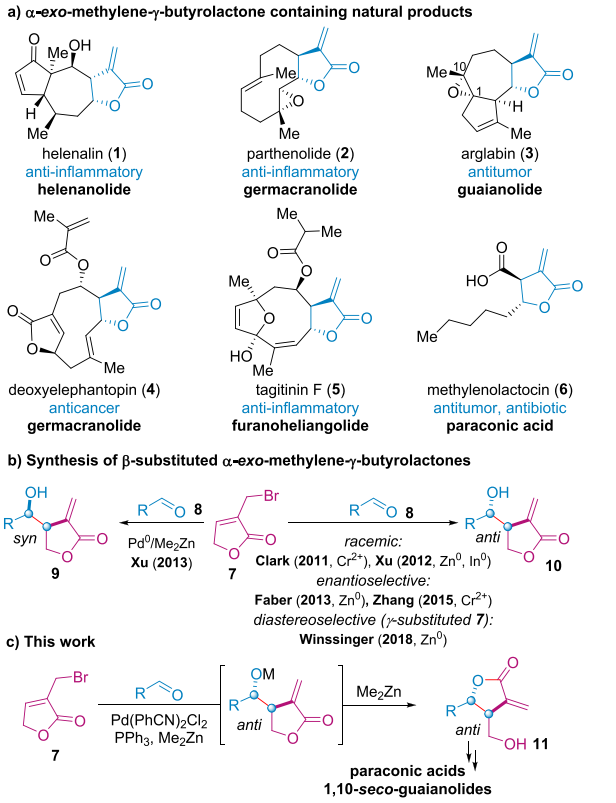
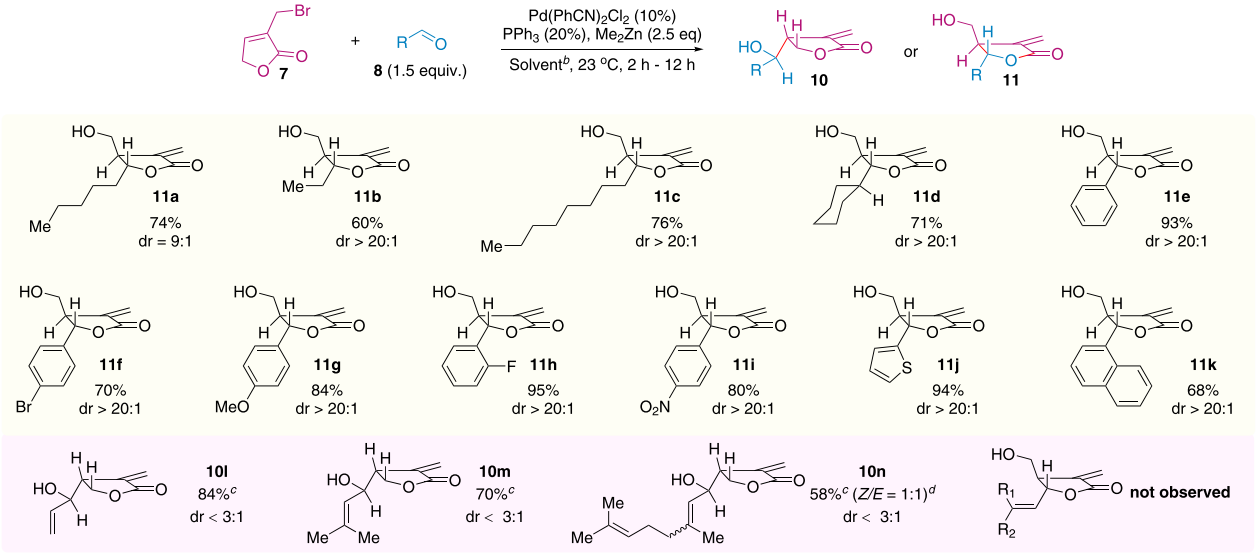


Figure 1. (a) Representative natural products containing *α-exo*-methylene-*γ*-butyrolactone. (b) Synthesis of *β*-substituted *α-exo*-methylene-*γ*-butyrolactones with a *syn*- or *anti*-configuration. (c) Our synthesis of *β,γ*-disubstituted *α-exo*-methylene-*γ*-butyrolactone with an *anti*-configuration.

did proceed through the translactonization. It is worth noting that low diastereomeric ratios (dr < 3:1) were obtained for **10l–n**. Based on the observation that the dr decreased with the extension of the reaction time, the low ratio probably

Scheme 2. Reaction Scope of the Barbier Allylation/Translactonization Sequence[a]



[a]On a 0.1 mmol scale. Yields of the product after purification. The dr is expressed as the ratio between *trans*- and *cis*-products as determined by ^{1}H NMR. [b]PhMe for aromatic aldehydes, THF for aliphatic aldehydes. [c]No translactonization, even with 5 eq of Me_2Zn at 30 °C. [d]A 1:1 *Z/E* isomer of the aldehyde was used as the starting material, and the reaction scale was 2.0 mmol.

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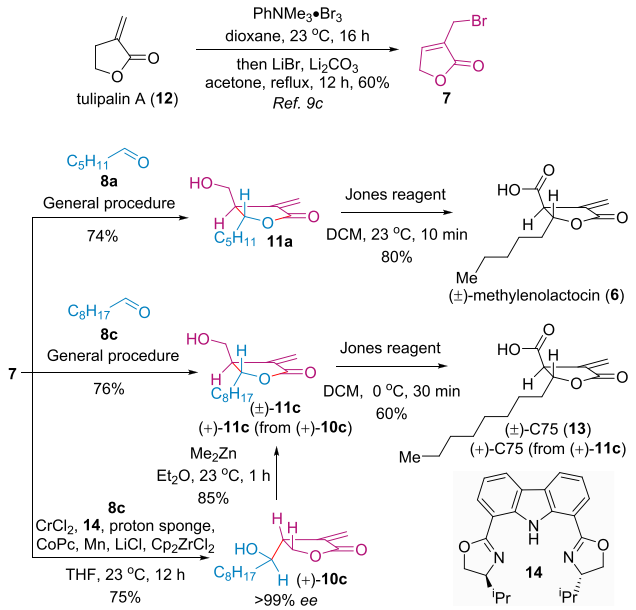
Org. Lett. 2021, 23, 969–973

resulted from the instability of the product under the reaction condition.

This sequence was next harnessed to synthesize the natural product (±)-methylenolactocin in three steps (Scheme 3, **6**).

Scheme 3. Synthesis of Paraconic Acids 6 and 13

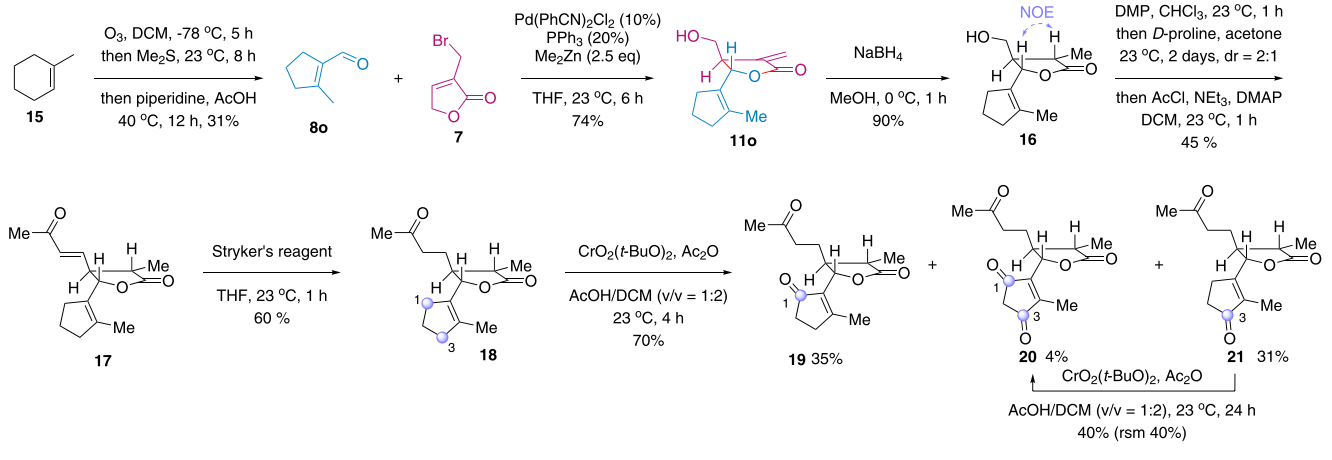


Starting with the bromolactone **7** that was prepared from commercially available tulipalin A (**12**)[9c] and hexanal (**8a**), the general procedure[16] afforded the addition product and the subsequent translactonization in a 74% yield. The oxidation of the primary alcohol to the corresponding acid was achieved with a Jones oxidation in an 80% yield to obtain (±)-methylenolactocin (**6**). The synthetic material matched the data reported for the natural product (^{1}H and ^{13}C NMR).[9a,d,17] This simple three-step protocol could also be used to obtain (±)-C75 (**13**, Scheme 3), an inhibitor of fatty acid synthase (FAS) that leads to profound weight loss and feeding inhibition in both high-fat diet wild-type obese and leptin-deficient *ob/ob* mice as well as to growth inhibition in tumors.[18] Based on the fact that the translactonization can be performed after the addition and that asymmetric Cr(II)-mediated allylation procedures are known,[9d] we applied this sequence to the stereoselective synthesis of C75. Treatment of nonanal (**8c**) and bromolactone **7** with $CrCl_2$ and the catalytic ligand **14** afforded (+)-**10c** in a 75% yield and excellent ee (>99%). Treatment of the product with dimethylzinc followed by a Jones oxidation afforded (+)-C75.

Finally, this allylation rearrangement sequence was applied to the synthesis of 1,10-*seco*-guaianolides 3-deshydroxy-*iso*-*seco*-tanapartholide (**19**) from *Achillea ligustica*[19] and 1,10-dioxo-1,10-deoxy-1,10-secogorgonolide (**20**) from *Artemisia gorgonum* (Scheme 4).[20] Aldehyde **8o** was synthesized from commercially available alkene **15** using slight modifications of a previously reported protocol.[21] Treatment of this aldehyde with bromolactone **7** under the palladium allylation condition with an excess of dimethyl zinc cleanly afforded the desired transesterified product **11o**. The reduction of the conjugated alkene with $NaBH_4$ gave a single diastereoisomer **16**. The oxidation of the primary alcohol, followed by a proline-catalyzed aldol condensation[22] and subsequent β-elimination by acylation, afforded the conjugated ketone **17**. The reduction of the α,β-unsaturated double bond using Stryker's reagent yielded **18**, which was submitted to the allylic oxidation condition ($CrO_2(Ot\text{-}Bu)_2$)[23] to obtain a mixture of three compounds (**19**-**21**); both single allylic oxidation products **19** and **21** were the major products. Of note, this six-step sequence furnished the first total syntheses of 1,10-*seco*-guaianolides **19** and **20** without any protecting group manipulations. In both cases, the spectroscopic data fully matched those of the natural isolate.[24] Interestingly, the C3-oxidized product **21** could be further transformed to natural product **20** under the same oxidation conditions.

In conclusion, a palladium-catalyzed Barbier allylation/translactonization cascade reaction was established for the rapid construction of β,γ-disubstituted α-methylene-γ-butyrolactone. Dimethyl zinc played significant roles in both steps for the umpolung of π-allylpalladium as a nucleophile and the promotion of a Lewis acid-mediated translactonization. This sequence showed a broad substrate scope and was further harnessed for the successful synthesis of two paraconic acids in three steps and the first total synthesis of two 1,10-*seco*-guaianolides in six steps without any protecting group manipulations. Finally, this methodology should be applicable in the total synthesis of other α-*exo*-methylene-γ-butyrolactone-containing natural products, especially sesquiterpene

Scheme 4. First Protecting-Group-Free Total Synthesis of 1-10-*seco*-Guaianolides 19 and 20



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lactones. This work also establishes that the *syn*-addition product **9** cannot be obtained using a palladium-catalyzed reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04165.

Experimental details, compound characterization, and chiral HPLC and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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(24) See Supporting Information (S4-S5, Table S2-S3) for details.

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