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# Palladium-Catalyzed Decarbonylative Dehydration for the Synthesis of α-Vinyl Carbonyl Compounds and Total Synthesis of (−)-Aspewentins A, B, and C**

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***Abstract:*** *The direct α-vinylation of carbonyl compounds to form a quaternary stereocenter is a challenging transformation. It was discovered that δ-oxocarboxylic acids can serve as masked vinyl compounds and be unveiled by palladium-catalyzed decarbonylative dehydration. The carboxylic acids are readily available through enantioselective acrylate addition or asymmetric allylic alkylation. A variety of α-vinyl quaternary carbonyl compounds are obtained in good yields, and an application in the first enantioselective total synthesis of (−)-aspewentins A, B, and C is demonstrated.*

An all-carbon quaternary center bearing an ethylene substituent is a common structural motif in many natural products (Figure 1).[1] An important approach to the construction of this unit is the α-vinylation of carbonyl compounds, and two general methods have been developed. One is the direct coupling of an enolate nucleophile with a vinyl electrophile such as an alkenyl ether,[2] vinyl bromide,[3] or acetylene itself.[4,5] Although this approach can be extended to alkenylations as well, and asymmetric versions are known,[3a,c,4c] the scope of the enolate nucleophile is generally limited to 1,3-dicarbonyl compounds[4] or those with only one enolizable position.[2,3,5b] A second tactic involves addition of the enolate nucleophile to a vinyl surrogate such as vinyl sulfoxide,[6] (phenylseleno)acetaldehyde,[7] or ethylene oxide,[8] followed by elimination. However, there are few reports of stereoselective additions that form the quaternary stereocenter,[9] and none are catalytic or enantioselective. Because of these constraints, even the simplest 2-methyl-2-vinylcyclohexanone (**7**) is not known as a single enantiomer in the literature.

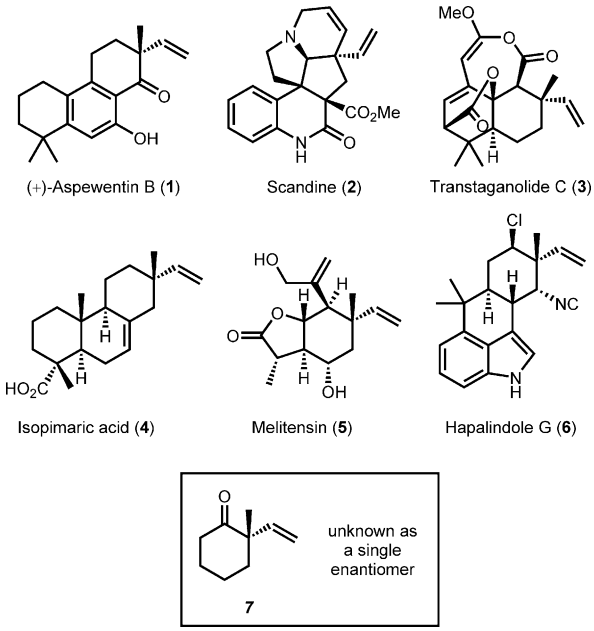
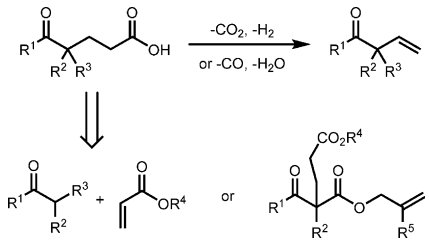



***Figure 1.*** Natural products with ethylene substituents.

We envisioned an alternative approach to access α-vinyl carbonyl compounds, by employing a decarboxylative elimination of δ-oxocarboxylic acids (Scheme 1). These acids may be prepared by numerous methods, including addition of an enolate nucleophile to an acrylate acceptor[10] and palladium-catalyzed allylic alkylation.[11] Importantly, these two methods allow the enantioselective construction of the requisite quaternary stereocenter.




***Scheme 1.*** Decarboxylative approach to vinylation.

Recently, we reported on the palladium-catalyzed decarbonylative dehydration of fatty acids to form terminal olefins.[12] Because of the importance of α-vinyl carbonyl compounds and the challenges in their preparation, we

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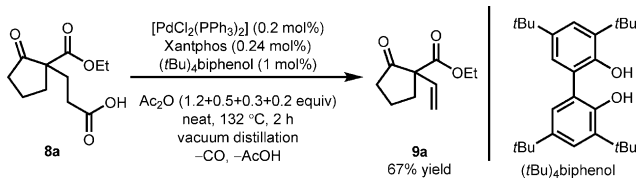
became interested in applying our decarbonylative dehydration chemistry as an alternative strategy to α-vinylation. Since the carboxylic acid, which bears a quaternary center two atoms away from the reactive carboxy group, is more hindered than a simple fatty acid, we expected that the reaction conditions would need to be tuned for this particular class of substrates. Additionally, from a practical standpoint, our previous studies were typically conducted on 5 grams of the fatty acid substrate without solvent, under vacuum distillation conditions. Thus, a smaller-scale alternative for implementation on laboratory scale and in the context of multistep organic synthesis would need to be developed.

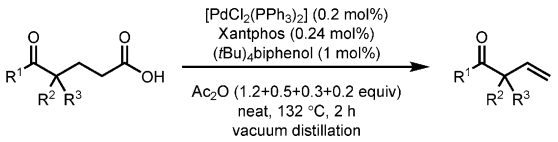
At the outset of our investigation, we prepared the carboxylic acid **8a** and subjected it to modified palladium-catalyzed decarbonylative dehydration conditions, where slightly higher loadings of catalyst, ligand, and additive were employed (Scheme 2). We were pleased to isolate the vinyl cyclopentanone **9a** in 67% yield.[13] This result demonstrated that the steric bulk at the quaternary center does not significantly retard the reaction, but proximal functionality (e.g. the ketone) could alter the reaction pathway.

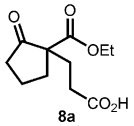
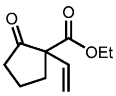
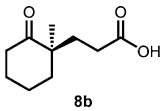
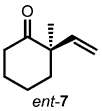
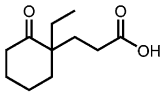
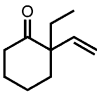
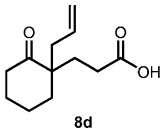
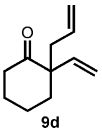
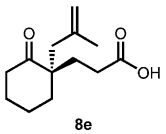
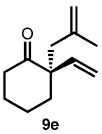
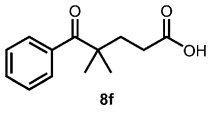
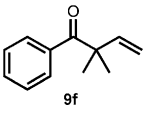
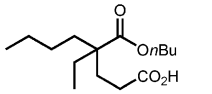
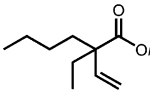
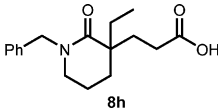
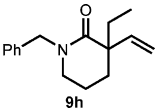
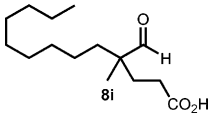
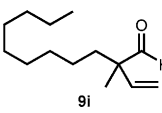
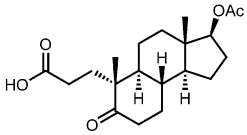
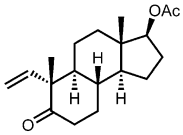



***Scheme 2.*** Decarbonylative dehydration of the δ-oxocarboxylic acid **8a**. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

With this exciting initial result in hand, we proceeded to investigate the scope of the reaction (Table 1). First, we synthesized (*R*)-3-(1-methyl-2-oxocyclohexyl)propanoic acid (**8b**) by an enantioselective d′Angelo Michael addition,[10] and subjected it to decarbonylative dehydration (entry 2). We were delighted to obtain the desired product, (*R*)-2-methyl-2-vinylcyclohexanone (*ent*-**7**), in 60% yield and 92% *ee*. Likewise, 2-ethyl-2-vinylcyclohexanone (**9c**) was prepared in a similar fashion. Carboxylic acids bearing allyl or 2-methallyl substituents were prepared by palladium-catalyzed allylic alkylation,[11] and they undergo decarbonylative dehydration smoothly to provide the corresponding 2-allyl-2-vinyl-substituted cyclohexanones **9d** and **9e** (entries 4 and 5), respectively, with the latter in 92% *ee* from the enantioenriched acid **8e**. It is worth noting that double-bond isomerization in the allyl moiety is negligible for **9d** and does not occur at all for **9e**. The acyclic keto acid **8f** is converted into the acyclic ketone **9f** in good yield (entry 6). Aside from keto acid substrates, we examined acids bearing other types of carbonyl functionalities (entries 7–10), and found that the α-vinyl ester **9g**, lactam **9h**, and aldehyde **9i** can all be prepared in good yields. More complex scaffolds such as **8j**, obtained by oxidative cleavage of testosterone,[14] also undergo the reaction to provide the vinylated tricycle **9j** (entry 11). While the reaction can be carried out in the absence of a solvent on a fairly large scale (5 mmol, entries 1–7), we found that for smaller scale synthesis it is more convenient to use *N*-methylpyrrolidinone (NMP) as a solvent along with slightly modified reaction conditions (entries 8–11).[15]

***Table 1:*** Decarbonylative dehydration of δ-oxocarboxylic acids (**8**).



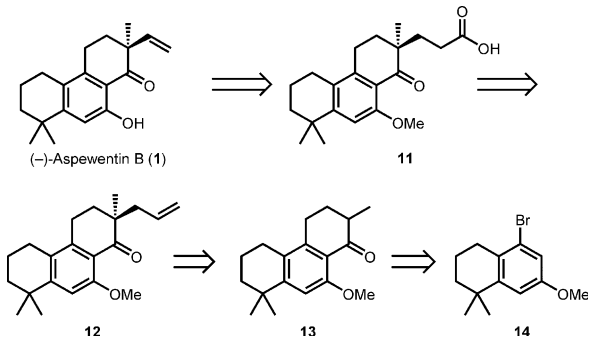

| Entry[a] | δ-Oxocarboxylic acid | Product | Yield and *ee* |
|---|---|---|---|
| 1 |  **8a** |  **9a** | 67% |
| 2 |  **8b** |  *ent*-**7** | 60%<br>92% *ee* |
| 3 |  **8c** |  **9c** | 66% |
| 4 |  **8d** |  **9d** | 54%[b] |
| 5 |  **8e** |  **9e** | 69%<br>92% *ee* |
| 6 |  **8f** |  **9f** | 75% |
| 7 |  **8g** |  **9g** | 50% |
| 8[c] | | | 51% |
| 9[c] |  **8h** |  **9h** | 57% |
| 10[c] |  **8i** |  **9i** | 77% |
| 11[c] |  |  | 41% |

[a] 5 mmol scale. [b] Isolated as a 95:5 mixture of desired product and internal olefin isomer. [c] Reaction conditions: 0.5 mmol substrate (1 equiv), benzoic anhydride (1.2 equiv), [$PdCl_2$(nbd)] (1 mol%), Xantphos (1.2 mol%), NMP (0.25 mL), 1 atm $N_2$, 132 °C, 3 h. nbd = 2,5-norbornadiene.

To further demonstrate the utility of our decarbonylative dehydration approach to vinylation, we embarked on a total synthesis of aspewentin B (**1**, Figure 1), a norditerpene natural product isolated from *Aspergillus wentii*.[16,17] This

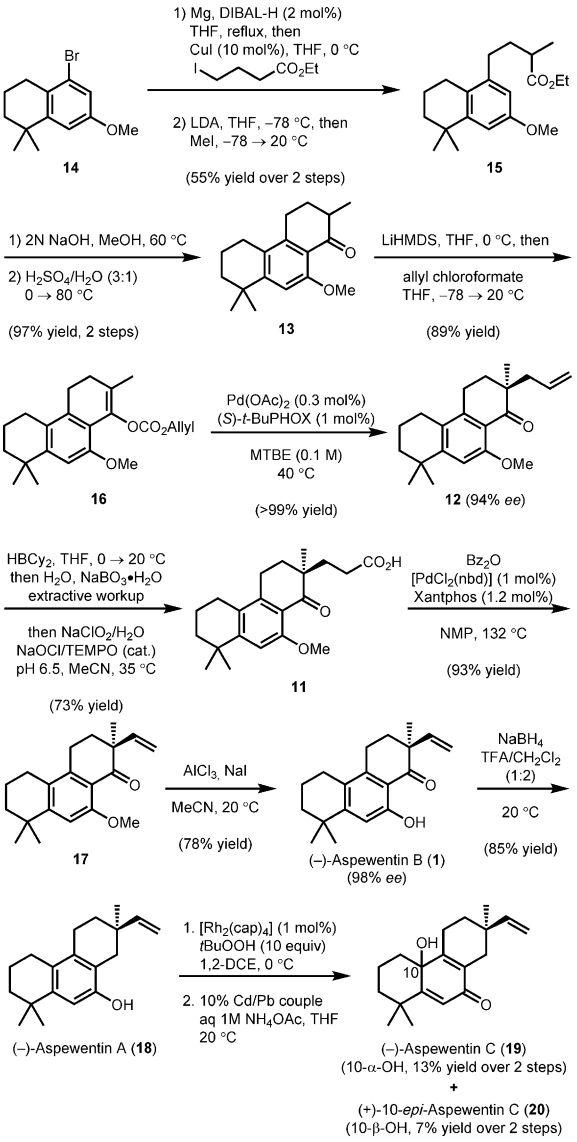
terpenoid contains an α-vinyl quaternary cyclohexanone scaffold, and is therefore ideally suited for our chemistry. Retrosynthetically, we envisioned that the vinyl group could be formed by decarbonylative dehydration of the δ-oxocarboxylic acid **11**, which might be obtained by elaboration of the allyl ketone **12** (Scheme 3).[18] The quaternary stereocenter would be set by palladium-catalyzed enantioselective allylic alkylation of the tricyclic ketone **13**, which could be constructed from the known aryl bromide **14**.[19]




***Scheme 3.*** Retrosynthetic analysis of (−)-aspewentin B.

We commenced our total synthesis by copper-catalyzed coupling of a Grignard reagent derived from **14** with ethyl 4-iodobutyrate (Scheme 4).[20] α-Methylation of the coupled product produces the ester **15**, which was saponified and then cyclized to form the tricyclic ketone **13**. The ketone was converted into the corresponding allyl enol carbonate (**16**), which was then subjected to palladium-catalyzed enantioselective decarboxylative allylic alkylation to afford the allyl ketone **12** in nearly quantitative yield and 94% *ee*. Interestingly, the allylic alkylation reaction proceeds efficiently with a low palladium catalyst loading, employing a new catalytic protocol recently developed by our group.[21] Only 2.7 mg of $Pd(OAc)_2$ is needed for a reaction of 1.42 grams of starting material (**16**) to deliver 1.25 grams of allyl ketone product (**12**). Hydroboration/oxidation of the terminal olefin of **12**, and further oxidation, delivers **11** in 73% yield.[18] Gratifyingly, palladium-catalyzed decarbonylative dehydration[22] furnishes the α-vinyl ketone **17** in 93% yield.[23] Removal of the *O*-methyl group provides (−)-aspewentin B (**1**) in 78% yield.[24] Thus, (−)-aspewentin B (**1**) was synthesized in nine steps and 25% overall yield from known starting materials. With **1** in hand, two other natural products of the aspewentin family can also be accessed. Reduction of the ketone moiety of **1** furnishes (−)-aspewentin A (**18**) in 85% yield.[25] Oxidation of the phenol in **18** affords (−)-aspewentin C (**19**) in 13% yield and (+)-10-*epi*-aspewentin C (**20**) in 7% yield, over two steps.[26]

In summary, we have developed a new approach to access α-vinyl quaternary carbonyl compounds by palladium-catalyzed decarbonylative dehydration of δ-oxocarboxylic acids. A variety of acids with different scaffolds and functional groups can be transformed into the corresponding α-vinyl carbonyl compounds without erosion of the stereointegrity of the neighboring quaternary center. We have also applied the method to the first enantioselective total synthesis of (−)-aspewentins A, B, and C. Further applications of this transformation in natural product synthesis are currently ongoing in our lab and will be reported in due course.




***Scheme 4.*** Total synthesis of (−)-aspewentin A, B, and C. cap = caprolactamate, DCE = 1,2-dichloroethane, DIBAL-H = diisobutylaluminum hydride, HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide, MTBE = methyl *tert*-butyl ether, NMP = *N*-methylpyrrolidone, PHOX = phosphinooxazoline, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

**Keywords:** enantioselectivity · natural products · olefination · palladium · total synthesis

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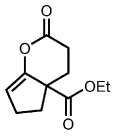
[13] The cyclic lactone **10** was also isolated in 20% yield as the major byproduct. Byproducts of this type are observed in cases where cyclic ketones possess an enolizable position.




**10**

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[15] The small-scale reactions were performed under 1 atm $N_2$ (no distillation). Acetic anhydride was found to be unsuitable under such conditions, while benzoic anhydride proved to be optimal.

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[17] While the natural product has (+) stereochemistry, we synthesized the (−) enantiomer because of the ready availability of the (*S*)-*t*BuPHOX ligand.

[18] The enantioselective Michael addition does not work for 1-tetralone substrates. For details, see: J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459 – 505.

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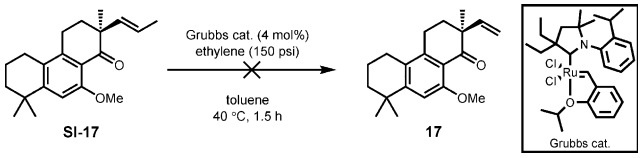
[22] Decarbonylative dehydration of **11** using $Ac_2O$ under standard vacuum distillation conditions results in no conversion; the reaction mixture solidifies upon distillation of AcOH.

[23] An alternative route from the allyl ketone **12** to vinyl ketone **17** involves isomerization of the double bond to the internal position followed by ethenolysis. While the isomerization (i.e., **12**→**SI-17**) proceeded smoothly using the protocol developed by Nishida and co-workers (M. Arisawa, Y. Terada, M. Nakagawa, A. Nishida, *Angew. Chem. Int. Ed.* **2002**, *41*, 4732 – 4734; *Angew. Chem.* **2002**, *114*, 4926 – 4928) to afford the internal olefin **SI-17**, attempts at ethenolysis of the resulting internal olefin were unsuccessful, likely a result of the steric bulk at the adjacent quaternary center. See the Supporting Information for details.




[24] Spectroscopic data ($^1$H and $^{13}$C NMR) and exact mass of the synthetic compound matches those of natural (+)-aspewentin B. The optical rotation, however, is significantly different (synthetic compound: $[\alpha]_D^{25}$ −90.5 (*c* 0.20, MeOH, 98% *ee*); natural product: $[\alpha]_D^{20}$ +23.3 (*c* 0.20, MeOH)). HPLC analysis showed the synthetic compound to be of 98% *ee*. Based on the stereoselectivity of the Pd-PHOX catalyst in previous examples, we reasoned that the absolute configuration of our synthetic compound is opposite to that of the natural product, and thus the sign of optical rotation is correct. The difference in magnitude may arise from the possibility that the natural product is a scalemic mixture (i.e. not enantiopure). For a review on non-enantiopure natural products, see: J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem. Int. Ed.* **2012**, *51*, 4802 – 4836; *Angew. Chem.* **2012**, *124*, 4886 – 4920. Another possibility is that the isolated natural product contained a small amount of impurity which had a large effect on the optical rotation.

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# Communications

## Natural Products

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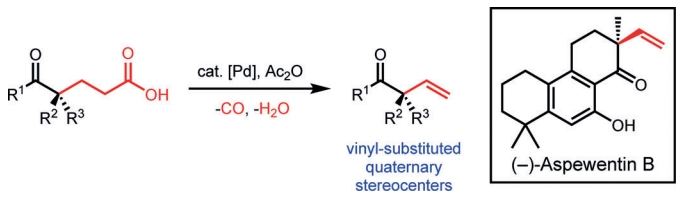
Palladium-Catalyzed Decarbonylative Dehydration for the Synthesis of α-Vinyl Carbonyl Compounds and Total Synthesis of (−)-Aspewentins A, B, and C




**Vinyl unveiled**: It is described that δ-oxocarboxylic acids can serve as masked vinyl compounds and be unveiled by Pd-catalyzed decarbonylative dehydration to enable the α-vinylation of carbonyl compounds to form a quaternary stereocenter. A variety of α-vinyl quaternary carbonyl compounds are obtained in good yields, and an application in the first enantioselective total synthesis of (−)-aspewentins A–C is demonstrated.