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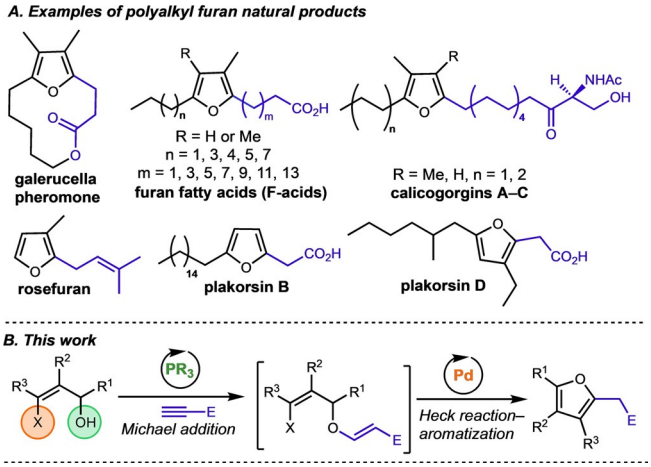
Homogeneous Catalysis

Unified Approach to Furan Natural Products via Phosphine-Palladium Catalysis

*Violet Yijang Chen and Ohyun Kwon**

Abstract: *Polyalkyl furans are widespread in nature, often performing important biological roles. Despite a plethora of methods for the synthesis of tetrasubstituted furans, the construction of tetraalkyl furans remains non-trivial. The prevalence of alkyl groups in bioactive furan natural products, combined with the desirable bioactivities of tetraalkyl furans, calls for a general synthetic protocol for polyalkyl furans. This paper describes a Michael–Heck approach, using sequential phosphine-palladium catalysis, for the preparation of various polyalkyl furans from readily available precursors. The versatility of this method is illustrated by the total syntheses of nine distinct polyalkylated furan natural products belonging to different classes, namely the furanoterpenes rosefuran, sesquirosefuran, and mikanifuran; the marine natural products plakorsins A, B, and D and plakorsin D methyl ester; and the furan fatty acids 3D5 and hydromumiamicin.*



Scheme 1. Examples of polyalkyl furan natural products and reaction design.

Introduction

Furan is a structural motif in a wide variety of bioactive natural products,[1] pharmaceuticals,[2] and useful intermediates in organic synthesis.[3] Polyalkyl furans, in particular, feature prominently in bioactive natural products (Scheme 1 A), including the galerucella pheromone;[4] calicogorgins A–C;[1d] furan fatty acids (F-acids),[5] potent antioxidants and radical scavengers that protect polyunsaturated fatty acids from lipid peroxidation; rosefuran,[6] the fragrant component of highly prized rose oil; and plakorsins D[7] and B,[8] cytotoxic F-acid derivatives isolated from the marine sponge *P. simplex*.

Although C2/C5-functionalization of furans can be achieved quite readily through metalation or electrophilic aromatic substitution,[9] the regioselective construction of highly functionalized furans poses a challenge. Among myriad methods available for the syntheses of tetrasubstituted furans, the overwhelming majority provide carbonyl-,[10] thioalkyl-,[11] halo-,[12] amino- and aryl-substituted[13] furans, but very few enable direct access to the tetraalkyl furans[14] that feature prominently in biologically important compounds (e.g., the F-acids). Notably, none of the three known syntheses of tetraalkyl furans[14] have, to the best of knowledge, ever provided furans with four non-identical alkyl substituents. Given the prevalence and desirable bioactivities of polyalkyl furans and the relative paucity of aryl substituents in furan-containing natural products,[15] it would be useful to have the ability to prepare polyalkyl furans efficiently.

(*Z*)-3-Halo-2-propen-1-ols are versatile substrates that can be obtained rapidly and stereoselectively from readily available propargyl alcohols and alkynoates through hydro/carbometalation-iodinolysis and hydroiodination-reduction sequences, respectively.[16] Having both hydroxyl and vinyl halide functionalities, we have found that they can be integrated seamlessly into sequential phosphine-palladium catalysis, wherein initially the OH group undergoes phosphine-catalyzed (*E*)-selective Michael addition to activated alkynes to give vinyl ether intermediates,[17a–c] which then undergo sequential Heck cyclization and spontaneous aromatization to give highly substituted furans (Scheme 1 B). The phosphine organocatalyst for the Michael addition acts as a ligand in the Heck reaction. The resulting (alkoxycarbonyl)alkyl side chain can then be transformed into other functional groups and homologated.[18–20] Using appropriately substituted (*Z*)-β-halo allylic alcohols, this approach becomes a general method for the synthesis of various bioactive polyalkyl furans from readily accessible precursors.

Results and Discussion

Our investigation of the Michael–Heck reaction began with optimization of the Michael addition between the β-iodoallylic alcohol **1m** and methyl propiolate (Supporting

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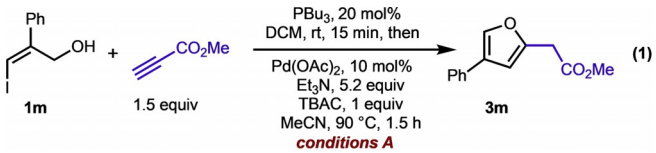
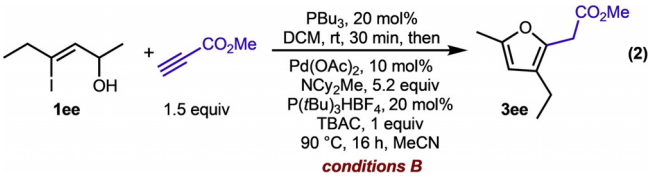
Information, Table S1). The more nucleophilic PBu_3 was superior to PPh_3 at accelerating the Michael reaction, while nonpolar solvents were preferred over polar ones, delivering the Michael adduct in 96% yield. Next, we examined the Heck reaction using the optimized conditions for the Michael addition (Supporting Information, Table S2). A screen of various bases revealed that Et_3N containing 1% water was optimal (Supporting Information, Table S3).[21] Toluene and MeCN were superior to dioxane as solvents, and Pd^{II} catalysts outperformed Pd^0 species. The presence of the phase-transfer agent tetrabutylammonium chloride (TBAC) was essential.[22] Thus, the use of non-anhydrous Et_3N and catalytic $Pd(OAc)_2$ in MeCN provided the furan **3m** in 97% yield [Eq. (1)].



(1)

With these optimized conditions in hand, we explored the substrate scope of the Michael–Heck reaction (Table 1). Under conditions A, we obtained the 2-substituted furan **3a** in 94% yield. These conditions were also compatible with both C3-alkyl and -aryl groups, delivering the 2,3-disubstituted furans **3a**–**3k** in good yields (53–90%). Elevated temperatures were required in the cases of the bulky 3-isopropyl- and 3-*tert*-butyl-substituted furans **3c** and **3d** (conditions A1). Notably, potentially reactive allyl and prenyl groups were inert to the Heck conditions, delivering **3e** and **3f**, respectively, in good yields. While both electron-donating and -withdrawing substituents on the C3-phenyl ring were tolerated, the reaction was sensitive to steric effects, with *meta* substituents (**3j**, **3k**) giving substantially lower yields than *para* (**3h**, **3i**) ones. A similar trend occurred among the 2,4-disubstituted furans, where C2-phenyl compounds containing *para* electron-withdrawing (**3o**) and -donating (**3p**) groups outperformed an *ortho*-substituted one (**3n**). While both C4-alkyl (**3l**) and -aryl (**3m**) groups were compatible, the use of 3-butyn-2-one (**3l′**, **3m′**) and ethynyl phenyl ketone (**3m″**) in place of methyl propiolate required slow addition of the alkyne (conditions A2) to prevent rapid polymerization of the Michael acceptor under phosphine catalysis. The ease with which the starting (*Z*)-3-halo-2-propen-1-ol could be functionalized enabled facile access to both 2,3- and 2,4-functionalized furans, which are difficult to obtain regioselectively when using conventional methods.[23] The standard conditions A were also applicable for the synthesis of 2,5-disubstituted furans, where C5-alkyl (**3q**, **3r**), -cycloalkyl (**3s**, **3t**), and -aryl (**3v**–**3x**) groups were all incorporated. No opening of the cyclopropyl ring (**3s**) occurred, and both bulky cyclohexyl (**3t**) and 1-naphthyl (**3x**) groups were compatible. Plakorsin A,[8a] an F-acid derivative from the marine sponge *P. simplex*, was obtained in 86% yield.

We turned our attention to the preparation of tri- and tetrasubstituted furans. While conditions A1 delivered the aryl-containing trisubstituted furans **3y**, **3bb**, and **3gg** in good yields, they failed for di- or trialkyl-substituted substrates. Because conditions A worked well for the preparation of furans containing at least one electron-withdrawing group, we attempted to make the Michael acceptor more electron-deficient (Supporting Information, Scheme S5), but detected no product and obtained copious amounts of polymerized Michael acceptor.[17c] Intrigued by Fu's report on the use of air-stable trialkylphosphonium salts for various cross-couplings of deactivated aryl chlorides and bromides,[24] we adapted those conditions for our Michael–Heck reaction [Eq. (2)].



(2)

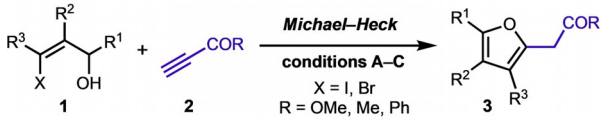
Using $P(t\text{-}Bu)_3HBF_4$ along with Cy_2NMe as the base, we prepared trialkyl furans with fused cycloalkyl (**3z**) and linear alkyl (**3cc**, **3dd**, **3ee**, **3hh**) substituents in moderate to good yields. Plakorsin D methyl ester,[7] a polyketide isolated from the marine sponge *P. simplex*, was obtained in 64% yield. Significantly, the medicinally relevant CF_3 group was compatible, furnishing the furan **3aa** in good yield.[25,26] While these conditions failed for the synthesis of tetraalkyl furans, a slight increase in the reaction temperature to 110 °C (from 90 °C for conditions B) and the use of $Pd_2(dba)_3$ as a catalyst enabled the preparation of tetraalkyl furans in good yields [Eq. (3)].

(3)

Whereas the presence of a C3-aryl unit led to a slightly diminished yield (**3ii**), tetraalkyl furans with either fused cycloalkyl (**3kk**) or linear alkyl (**3jj**, **3ll**) groups were prepared in good yields. In the cases of **3z** and **3kk**, we used a vinyl bromide substrate, further highlighting the versatility of this method. Finally, furans substituted with four different alkyl groups (**3mm**, **3nn**) could be prepared in good yields. To the best of your knowledge, this methodology is the first ever reported of result in the synthesis of furans bearing four different alkyl substituents. Among the more than 90 reports describing the syntheses of tetrasubstituted furans, only three have been amenable to the preparation of tetraalkyl furans,[14] and none of them to the synthesis of furans presenting four different alkyl groups. The compatibility of silyl ether groups is also significant, suggesting potential application of this method towards total synthesis of complex furan natural products.

Having demonstrated the wide substrate scope of the Michael–Heck reaction, we explored its applications in the

Table 1: Substrate scope of the Michael–Heck reaction.[a,b]



2,3-substitution

2-substitution

3a 94% *conditions A*

3b 90% *conditions A*

3c 73% *conditions A1*

3d 62% *conditions A1*

3e 72% *conditions A*

3f 67% *conditions A*

3g 77% *conditions A*

3h 72% *conditions A*

3i 71% *conditions A*

3j 53% *conditions A*

3k 58% *conditions A*

2,4-substitution

3l 82% *conditions A*

3m 97% *conditions A*

3n 53% *conditions A*

3o 87% *conditions A*

3p 84% *conditions A*

3l' 91% *conditions A2*

3m' 53% *conditions A2*

3m'' 46% *conditions A2*

2,5-substitution

3q 96% *conditions A*

3r 84% *conditions A*

3s 77% *conditions A*

3t 79% *conditions A*

3u (plakorsin A) 86% *conditions A*

2,5-substitution (cont'd)

3v 89% *conditions A*

3w 62% *conditions A*

3x 67% *conditions A*

2,3,4-substitution

3y 75% *conditions A1*

3z 96%[c] *conditions B*

2,3,5-substitution

3aa 77% *conditions A*

3bb 78% *conditions A1*

3cc 70% *conditions B*

3dd 81% *conditions B*

3ee 66% *conditions B*

3ff (plakorsin D methyl ester) 64% *conditions B*

2,4,5-substitution

3gg 79% *conditions A1*

3hh 93% *conditions B*

2,3,4,5-substitution

3ii 54% *conditions B*

3jj 75% *conditions C*

3kk 69%[c] *conditions C*

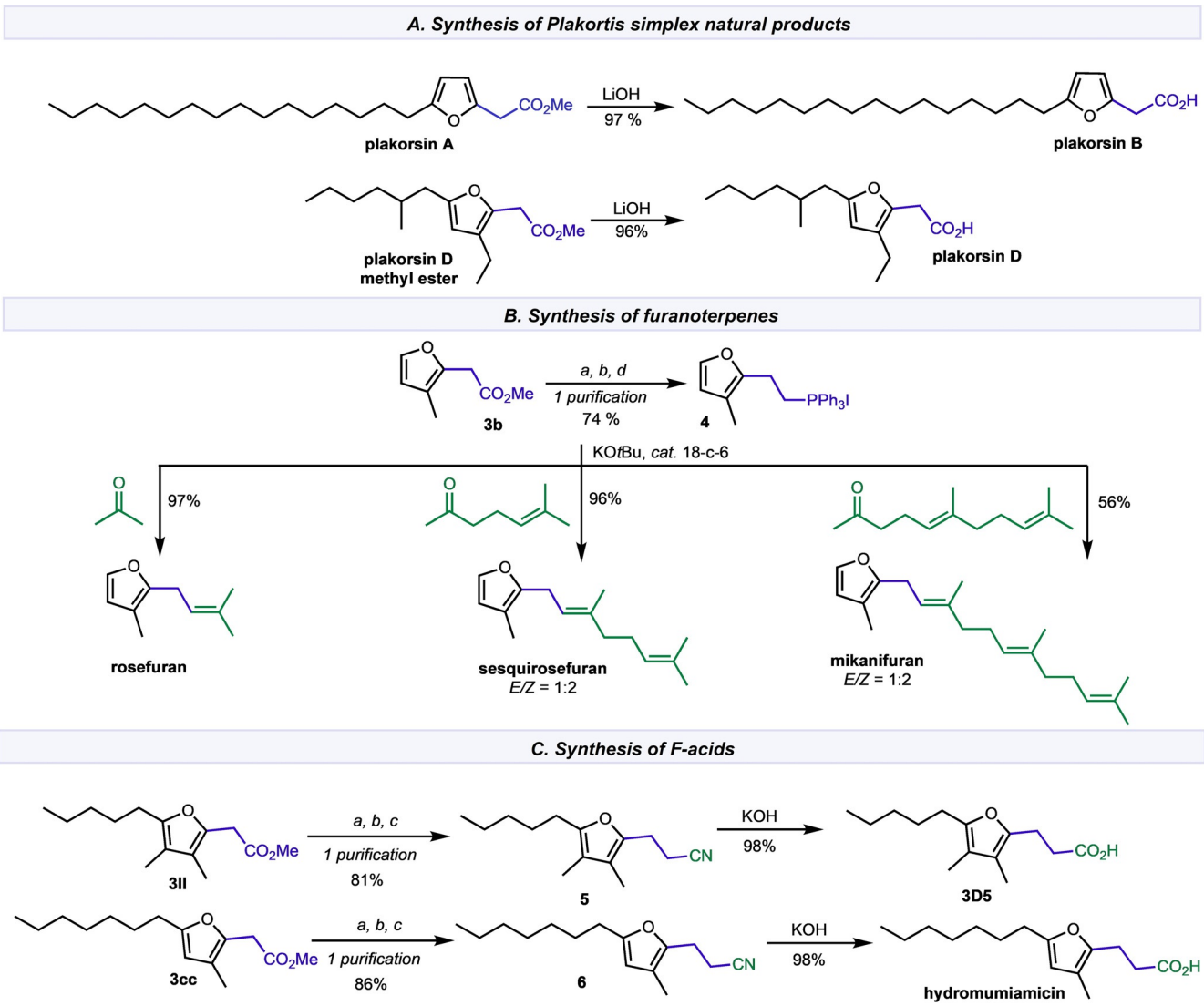
3ll 89% *conditions C*

3mm 86% *conditions C*

3nn 70% *conditions C*

[a] All reactions were performed under Ar using anhydrous solvents. [b] Isolated yields after flash-column chromatography. [c] X = Br.

total syntheses of bioactive furans (Scheme 2 A). Hydrolysis of plakorsin A produced plakorsin B, known to exhibit strong cytotoxicity against colon carcinoma (COLO-250) cells and weak activity against nasopharyngeal carcinoma (KB-16) cells.[8a] Previous approaches to plakorsins A and B have included Lewis acid-mediated 5-*endo*-dig cyclization of 3-alkyne-1,2-diols,[27] sequential functionalization of furan through lithiation/alkylation,[28] and electrophilic aromatic substitution of methyl 2-furylacetate[29] and 2-cyanomethylfuran,[29b,30] the latter of which suffered from highly variable yields (23–92 %). On the other hand, our Michael–Heck approach reliably furnished plakorsin A from methyl propio-



Scheme 2. Applications of products of Michael–Heck reactions to total syntheses of bioactive furan natural products Reaction conditions: a) $LiAlH_4$, Et_2O, 0 °C, 15 min. b) PPh_3, I_2, imidazole, THF, rt, 15 min. c) KCN, acetone/water, reflux, 16 h. d) PPh_3, neat, 1 h, 80–85 °C.

late in 62 % yield over three steps. Hydrolysis of plakorsin D methyl ester furnished plakorsin D-its first total synthesis.[31a]

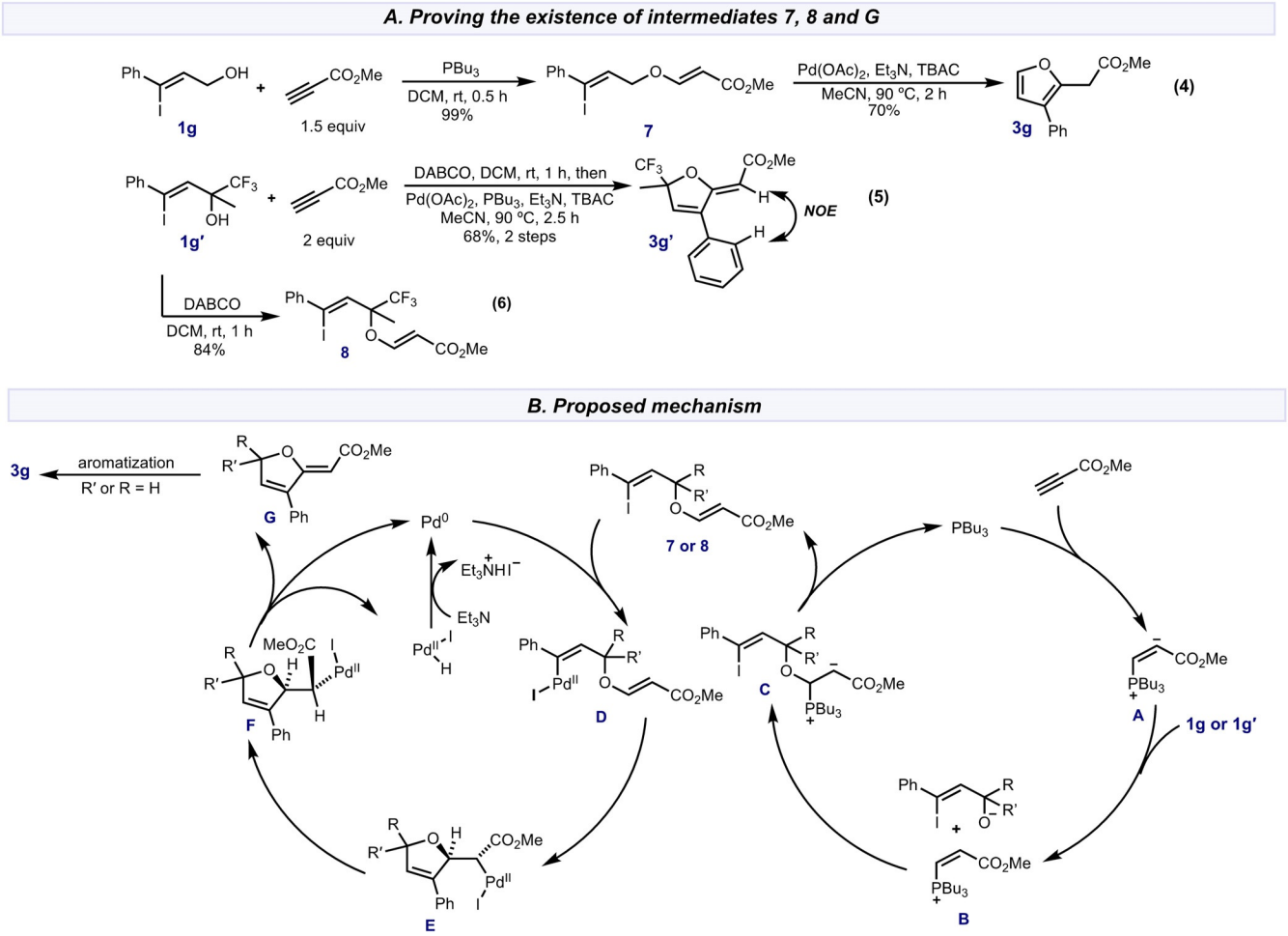
Next, we moved on to the synthesis of 2,3-disubstituted furanoterpenes (Scheme 2 B). Reduction of the ester group of the furan **3b** produced an alcohol intermediate,[32] which we transformed to a halide. Surprisingly, the bromide was unstable,[33] but the iodide proved to be robust and was converted smoothly to the phosphonium iodide **4** when using PPh_3 as the reaction solvent.[34] A subsequent Wittig reaction under Boden's conditions[35] furnished rosefuran in 97 % yield. To prevent complications resulting from lithiation of the free C5 position of **4**, we chose KO*t*Bu as the base. We used the same approach for the syntheses of sesquirosefuran[36] and mikanifuran.[37] In these cases, excess ketone and high reaction concentrations were necessary to prevent the formation of 3-methyl-2-vinylfuran as a side product (presumably resulting from E2 elimination of **4**).[38] Under these conditions, we obtained sesquirosefuran in 96 % yield as a mixture of *E*/*Z* isomers. Despite efforts to selectively obtain the *E*-isomer,[39] the inherent *Z*-selectivity of Wittig reactions with unstabilized ylides resulted in a mixture of isomers.[40] We also used these conditions to prepare mikanifuran in 56 % yield as a mixture of *E*/*Z* isomers. In addition to being used in fragrances and spices, rosefuran is also a female sex pheromone in the acarid mite, *Caloglyphus* sp., capable of triggering sexual excitation at less than 100 ng.[6a,b] While mikanifuran has no known biological activity, sesquirosefuran displays significant cytotoxicity against HeLa cells in vivo.[36] The commercial importance and biological activity of rosefuran has inspired several ingenious syntheses of it and related furanoterpenes. These strategies can be classified into alkylation, transition metal-catalyzed methods, functionalization of cyclic precursors, and cyclization of linear precursors.[41]

For the total synthesis of **3D5**, a unique F-acid found in the soft corals *S. glaucum* and *S. gemmatun* (Scheme 2 C), we employed a sequence of reduction, Appel reaction, and cyanation of the furan **3ll** to produce the nitrile **5**, which

underwent hydrolysis in 98% yield to give the F-acid.[42] Similarly, the furan **3cc** was converted into the nitrile **6**, which was hydrolyzed in 98% yield to produce hydromumiamicin,[43] an F-acid derivative in the actinomycete strain *Mumia sp.* YSP-2-79 with antimicrobial and antioxidant activity. While several syntheses have been reported of F-acids featuring long carboxyalkyl chains, our present total syntheses are the first for F-acids having a three-carbon carboxyalkyl chain.[44] While many efficient methods are available for the syntheses of 2,3-disubstituted furanoterpenes, F-acids, and their derivatives, only this present approach is applicable to the preparation of all three types of natural products.

To verify the reaction mechanism, we isolated the putative Michael adduct (*E*)-alkoxyacrylate[45] intermediate **7** and subjected it to the optimized Heck conditions, obtaining the furan **3g**, albeit in slightly diminished yield when compared with the one-pot procedure [Eq. (4)]. The nascent Michael–Heck adduct 2-furanylideneacetate **3g′** was also prepared when using the tertiary alcohol **1g′** [Eq. (5)]. Notably, only (*Z*)-2-[furan-2(5*H*)-ylidene]acetate **3g′** was isolated in 68% yield, supporting the occurrence of stereospecific syn-insertion and syn-elimination during the Heck process (see below). While the phosphine-catalyzed Michael addition of primary and secondary alcohols onto alkyl propiolates is well established, examples involving tertiary alcohols are extremely rare and often involve the use of more reactive PMe_3.[46] We found, however, that employing PMe_3 resulted in the rapid polymerization of methyl propiolate. Tejedor's insightful report on Lewis base-catalyzed addition of primary, secondary, and tertiary alcohols onto alkyl propiolates suggested that the increased basicity of a tertiary alcohol, as well as the decreased nucleophilicity of the corresponding tertiary alkoxide, made it unable to compete with the dimerization or polymerization of alkyl propiolates in the presence of amines or phosphine catalysts.[17c] To remedy this quandary, we positioned a pK_a-lowering CF_3-substituent onto the tertiary alcohol.[47] To our delight, we obtained the Michael adduct **8** from **1g′** in 84% yield. Having verified the feasibility of the DABCO-catalyzed Michael addition of acidic tertiary alcohols onto methyl propiolate, we then subjected **1g′** to the Heck conditions. Gratifyingly, the small amount of methyl propiolate dimer[48] formed did not interfere with the Heck reaction, and the (*Z*)-2-[furan-2(5*H*)-ylidene]acetate **3g′** was isolated in 68% yield. NOE correlations between the electron-deficient vinyl proton and the *ortho* phenyl protons confirmed the (*Z*)-geometry of **3g′**.

The observations described above underpin the following mechanism for our Michael–Heck reaction (Scheme 3B). Initially, tributylphosphine adds onto the electron-deficient



Scheme 3. Mechanistic investigations.

acetylene to produce the zwitterion **A**, which deprotonates the alcohol **1** to form the corresponding phosphonium alkoxide ion pair **B**. The alkoxide ion then adds onto the β-phosphonium enoate to produce the zwitterion **C**, which eliminates tributylphosphine to furnish the Michael adduct **7**/**8**. Subsequent oxidative addition of the Pd^0 complex leads to **D**, which undergoes *syn*-carbopalladation to produce the dihydrofuran intermediate **E**. After rotation about the C–C single bond, the resulting intermediate **F** undergoes stereospecific *syn*-β-hydride elimination to generate (*Z*)-2-[furan-2(5*H*)-ylidene]acetate **G**, which spontaneously undergoes aromatization to give the desired furan products when one of the C5 substituents is a hydrogen atom.

Conclusion

We have developed a Michael–Heck protocol for the versatile synthesis of furans of various substitution patterns from (*Z*)-3-halo-2-propen-1-ols and propiolates. Notably, this method produced, for the first time, furans substituted with four different alkyl groups. The C2-carboxymethyl group derived from the propiolate can then be used conveniently as a handle for further transformations. We have demonstrated the applicability of this new protocol through total syntheses of the *P. simplex* marine sponge natural products plakorsins A, B, and D and plakorsin D methyl ester; the furanoterpenes rosefuran, sesquirosefuran, and mikanifuran; and the F-acids 3D5 and hydromumiamicin. Employing (*Z*)-β-halo allylic alcohols, which are readily available, this method offers a general entry to the direct and regioselective syntheses of F-acids and other biologically important polyalkyl furans.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: furan natural products · furan synthesis · Heck reaction · Michael addition · phosphine–palladium catalysis

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[30] Ref [8c].

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