Organic LETTERS

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Stereoselective, Ag-Catalyzed Cyclizations To Access Polysubstituted Pyran Ring Systems: Synthesis of C_1–C_{12} Subunit of Madeirolide A

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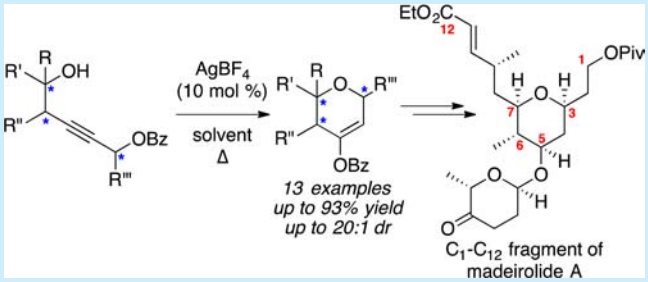
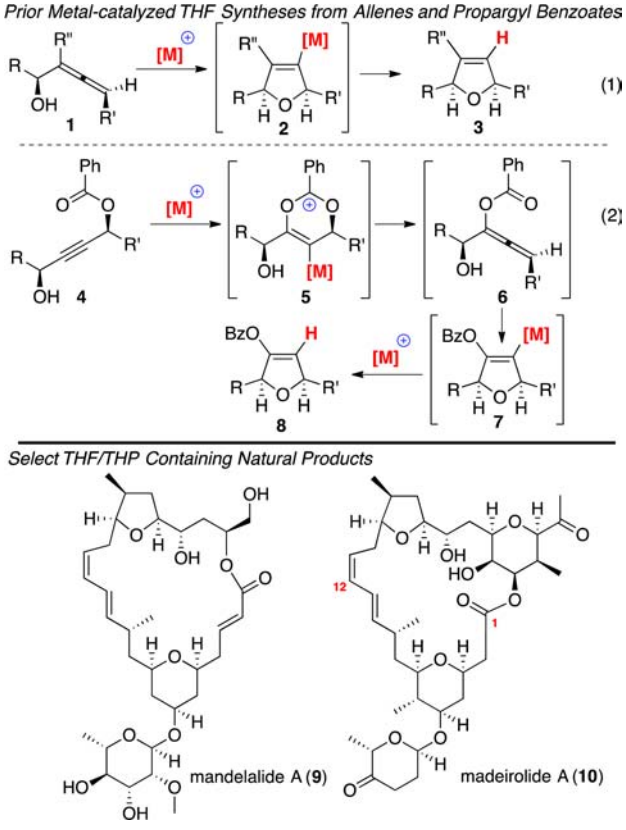
Supporting Information

ABSTRACT: The exploration into the scope of a silver-catalyzed cyclization (AgCC) of propargyl benzoates for accessing pyran ring systems has been reported. The impact of the degree of substitution, nature of the substitution on the carbon backbone/benzoate moiety, and stereochemistry has been evaluated. The application of this methodology to the synthesis of the C_1–C_{12} southern fragment of madeirolide A is disclosed.



Nature produces a diverse array of polyketide natural products that have shown interesting biological activity. Many of these polyketides contain stereodefined, polysubstituted tetrahydrofurans and tetrahydropyrans (Scheme 1). Consequently, a broad array of synthetic tools have been developed to access these structural classes,[1] including various transition-metal-mediated processes. The use of allenyl alcohols as suitable precursors has proven effective in metal-catalyzed (primarily Au and Ag) methods for accessing dihydrofurans (eq 1)[2] and dihydropyrans.[3] Our laboratory has had a long-standing interest in macrolides including those containing furan and pyran ring systems.[4] More recently, we have been focused on the potential of silver-catalyzed cyclizations (AgCCs) with propargyl benzoates for accessing furanyl ring systems (eq 2).[5] This work was inspired by Shigemasa and other pioneering authors in the area.[6,7] In these transformations, the propargyl benzoate **4** must first undergo metal-catalyzed rearrangement to an allenyl enol ether **6** which then undergoes a second metal-catalyzed process, this time a 5-*endo* cyclization to access a presumed vinyl metallo intermediate **7** which subsequently protodemetallates to give the final, dihydrofuranyl enol ether product **8**. We became intrigued by the potential of extending this concept to access tetrahydropyrans using the corresponding homopropargylic alcohols. Toste and co-workers demonstrated the potential of phenolic-containing propargylic benzoates for accessing enantioenriched benzopyrans.[8] Kotikalapudi and Swamy utilized highly unsaturated propargyl benzoate systems for access to dienyl pyran systems.[9] In our recent total synthesis of mandelalide A (**9**), we demonstrated the first example of using a AgCC to access a *cis*-disubstituted pyran moiety.[5c] Concurrent with our mandelalide A synthesis, Fürstner and co-workers reported a *exo*-cyclic version of this transformation in their synthesis of enigmazole A.[10] Herein, we disclose the exploration of a general method for accessing enol benzoate-containing dihydropyrans and its application to the

Scheme 1. Background of Metal-Catalyzed THF Synthesis and Select Natural Product Examples



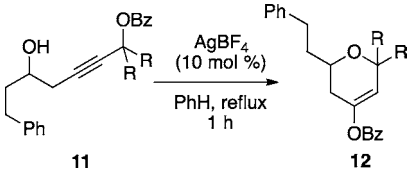
Received: February 11, 2016
Published: March 31, 2016

DOI: 10.1021/acs.orglett.6b00414
Org. Lett. 2016, 18, 1744–1747

synthesis of the C_1–C_{12} fragment of the antifungal macrolide madeirolide A (**10**).[11]

We first sought to explore the impact of substitution on the propargylic benzoate carbon[12] in the AgCC process (Table 1).

Table 1. Exploration of Scope of AgCC



11 **12**

entry	R	yield (%)
a	Me	73
b	Et	76
c	Ph	decomp
d	$-(CH_2)_4-$	89
e	$-(CH_2)_5-$	83
f	$-(CH_2)_2-O-(CH_2)_2-$	73
g[a]	H	decomp

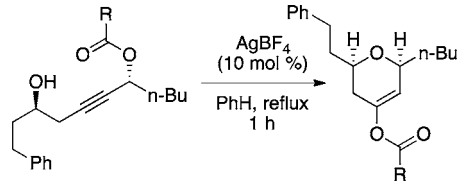
[a]This result was observed in refluxing toluene (3 h) and xylenes (1 h). No reaction was observed under refluxing benzene (4 h).

The optimum conditions for these cyclizations were in refluxing benzene. The reaction proceeded faster at higher temperatures (e.g., refluxing toluene or xylenes); however, slightly lower yields were typically observed (ca. 5–10% lower). We were pleased to see clean conversion with both the dimethyl benzoate **11a** and the diethyl variant **11b** to their desired products in 73% and 76% yield, respectively. Interestingly, the diphenyl benzoate **11c** proved problematic, as decomposition was observed under the reaction conditions. We attribute this outcome to the strong propensity of the benzoate moiety to ionize to the corresponding 3° carbocation which would be highly stabilized by the two phenyl substituents as well as the alkyne. Cyclic systems (e.g., **11d**–**11f**) worked smoothly to provide the spirocyclic products in good to excellent yields (73–89%). The absence of any substitution at the propargylic benzoate carbon was problematic as the primary benzoate **11g** led to no reaction under refluxing benzene conditions and decomposition at higher temperatures.

We next set out to study the impact of substituents on the benzoate moiety in the cyclization (Table 2). We focused on the disubstituted AgCC, as we recently demonstrated the utility of this transformation in our mandelalide A synthesis.[5c] These cyclization precursors were accessed from known chiral building blocks.[13] We observed a modest temperature dependent stereoerosion in the cyclization process. Interestingly, higher reaction temperatures appeared to have a slight, positive impact on the stereochemical outcome of the process. The use of more electron-rich benzoates (e.g., **13d**) led to an increase in the reaction rate, likely due to the increased nucleophilicity of the benzoate to attack the silver-activated alkyne (entries 10–12); however, a decrease in the overall selectivity was observed. In contrast, the use of a more electron-deficient benzoate (**13e**) led to dramatically lower yields and slightly reduced diastereoselectivity (entries 13–15).

Varying substitution of the carbon backbone led to interesting results (Scheme 2).[12] The use of a primary alcohol as the terminal nucleophile (compound **15**) in the AgCC worked smoothly and in high yield. This result is in contrast to the primary propargylic benzoate **11g** which led to decomposition. A series of cyclization precursors containing multiple stereochemistries were studied. The stereoselectivities on alcohols **17b**–**c** were modest (5–6:1 dr), but the reactions proceeded in generally good yields. Interestingly, the epimeric alcohol stereochemistry **19** did produce the expected *trans*-pyran ring **20**, but in low diastereoselectivity (2:1 dr). This example clearly demonstrates that significant stereochemical scrambling is occurring on a similar time frame to cyclization. The presence of a second propargylic stereocenter proved beneficial, leading to excellent stereoconversion (20:1 dr) for alcohol **21** to enol benzoate **22**; however, the formation of a dihydrofuran (DHF) byproduct **23** was also observed.[14] The use of tertiary alcohols produced nearly equal amounts of five- and six-membered products. Finally, the use of the stereochemically dense alcohol **27** did provide the target dihydropyran **28**.[14] Crude NMR indicated a similar DHF byproduct was also formed in nearly equal amounts (approximately 1:1); however, this presumed DHF compound proved too unstable to verify. Subsequent hydrolysis of the enol benzoate **28** provided the pyranone **29** in 20:1 dr.

Table 2. Exploration of Diastereoselective AgCC



13a R = Ph
13b R = o-Me-C_6H_4
13c R = p-Me-C_6H_4
13d R = p-OMe-C_6H_4
13e R = p-CF_3-C_6H_4

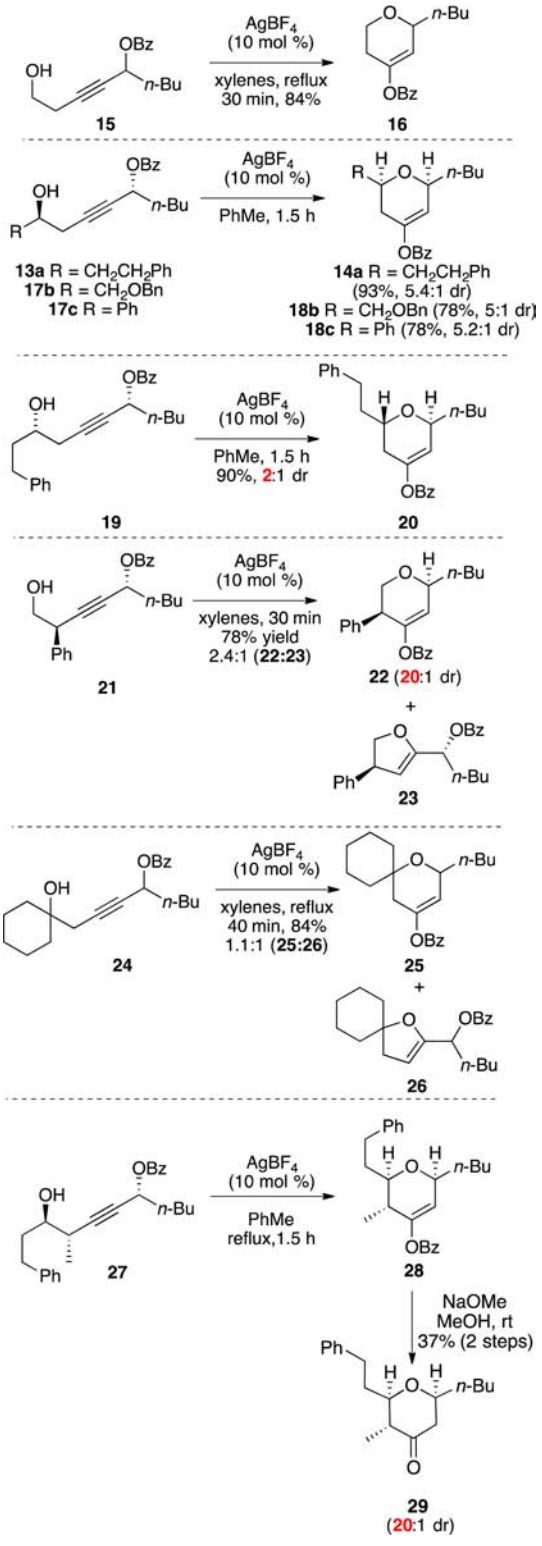
14a R = Ph
14b R = o-Me-C_6H_4
14c R = p-Me-C_6H_4
14d R = p-OMe-C_6H_4
14e R = p-CF_3-C_6H_4

entry	substrate	conditions	% yield (dr)
1	**13a**	PhH, reflux, 3.5 h	92 (4.6:1)
2	**13a**	PhMe, reflux, 1.5 h	93 (5.4:1)
3	**13a**	xylenes, reflux, 50 min	93 (5.5:1)
4	**13b**	PhH, reflux, 4 h	79 (4.2:1)
5	**13b**	PhMe, reflux, 5 h	87 (4.8:1)
6	**13b**	xylenes, reflux, 50 min	86 (4.6:1)
7	**13c**	PhH, reflux, 3.5 h	93 (3.8:1)
8	**13c**	PhMe, reflux, 1.5 h	94 (4.0:1)
9	**13c**	xylenes, reflux, 50 min	90 (4.3:1)
10	**13d**	PhH, reflux, 2.5 h	77 (2.6:1)
11	**13d**	PhMe, reflux, 1.5 h	93 (3.8:1)
12	**13d**	xylenes, reflux, 30 min	91 (3.8:1)
13	**13e**	PhH, reflux, 7 h	13 (3.0:1)
14	**13e**	PhMe, reflux, 5 h	45 (3.2:1)
15	**13e**	xylenes, reflux, 1 h	62 (3.5:1)

With a firm knowledge of the reaction scope, we applied the AgCC protocol to the synthesis of the C_1–C_{12} fragment of madeirolide A (Scheme 3). Starting from readily available vinyl iodide **30**[15] and alkyne **31**,[5b] Sonogashira cross-coupling generated the enyne **32** in good yield. Shi epoxidation of enyne **32** proceeded in excellent diastereoselectivity and good overall yield. Subsequent ring opening at the propargylic position was best accomplished using $LiAlMe_4/BF_3{\cdot}Et_2O$ to provide clean stereoconversion to alcohol **35**. We were pleased to see that the key AgCC proceeded in excellent diastereoselectivity to provide the enol *p*-methoxybenzoate **36** in >20:1 dr along with a minor amount of the undesired DHF **37** in an approximately 1.4:1 ratio (**36**:**37**). The *p*-methoxy

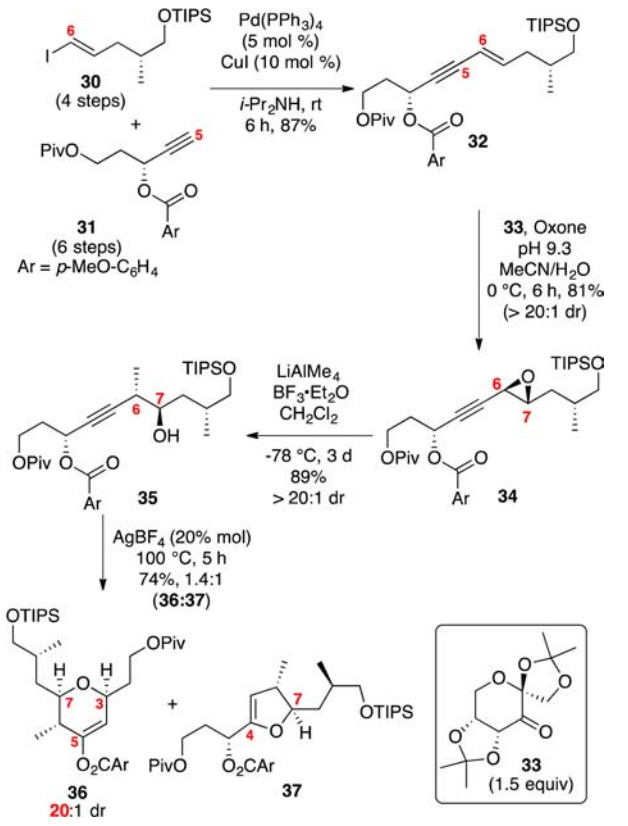
DOI: 10.1021/acs.orglett.6b00414
Org. Lett. 2016, 18, 1744–1747

Scheme 2. Exploration of Stereochemistry in AgCC



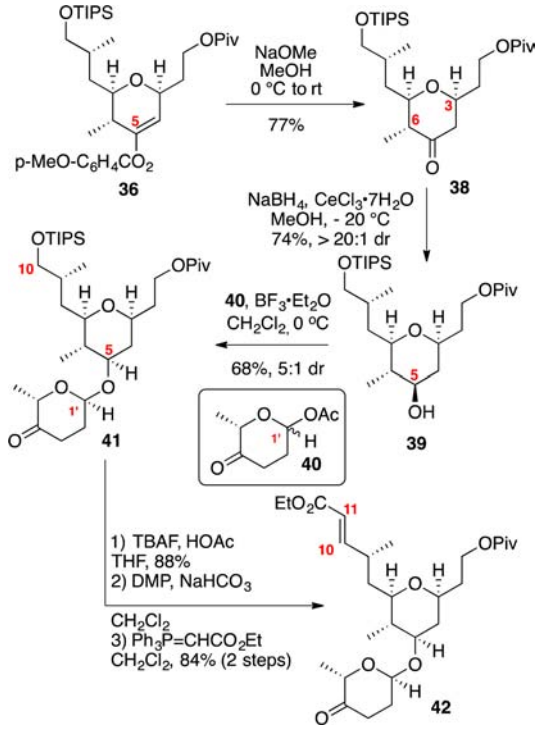
group on the aromatic ring of the benzoate was essential for obtaining reasonable yields. Interestingly, the DHF product[14] was formed in greater quantities at lower temperatures, indicating a higher activation barrier for isomerization of the propargylic benzoate to the allene as compared to direct cyclization by the alcohol to the activated alkyne. The DHF **37** proved unstable and decomposed partially under SiO_2 purification conditions and upon storage in $CDCl_3$.

Scheme 3. AgCC for Accessing the C_3–C_7 THP Ring in Madeirolide A



The completion of the southern, C_1–C_{12} fragment of madeirolide A is shown in Scheme 4. NaOMe cleavage[5c] of the enol benzoate revealed the desired ketone with no

Scheme 4. Synthesis of the C_1–C_{12} Subunit of Madeirolide A



DOI: 10.1021/acs.orglett.6b00414
Org. Lett. 2016, 18, 1744–1747

stereoerosion at C_3 or C_6. Stereoselective reduction of the C_5 ketone followed by attachment of the glycoside **40**[11b] provided product **41**. Finally, buffered TBAF deprotection of the C_{10} OTIPS ether followed by DMP oxidation and Wittig olefination introduced the key *trans* $C_{10,11}$ alkene **42**.

In summary, the scope of AgCC to access pyran ring systems has been explored. The impact of the degree of substitution, nature of substituents, and stereochemistry has been studied. Extension of this work to the synthesis of the southern, C_1−C_{12} subunit of madeirolide A has been demonstrated. Further work exploring the AgCC reaction and its application in synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00414.

Complete experimental procedures (PDF)

Copies of ^{1}H and ^{13}C spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by Oregon State University. K.W. acknowledges Tohoku Pharmaceutical University for fellowship support. We thank Professor Claudia Maier and Dr. Jeff Morré (OSU) for mass spectrometric data.

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(12) The synthetic routes for each one of the cyclization precursors provided in the Supporting Information.

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DOI: 10.1021/acs.orglett.6b00414
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