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Synthetic Methods

Highly *trans*-Selective Arylation of Achmatowicz Rearrangement Products by Reductive γ-Deoxygenation and Heck–Matsuda Reaction: Asymmetric Total Synthesis of (−)-Musellarins A–C and Their Analogues

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Abstract: Fully functionalized pyranuloses derived from Achmatowicz rearrangement (AR) are versatile building blocks in organic synthesis. However, access to *trans*-2,6-dihydropyrans from pyranuloses remains underexplored. Herein, we report a new two-step *trans* arylation of AR products to access 2,6-*trans*-dihydropyranones. This new *trans*-arylation method built on numerous plausible, but unsuccessful, direct arylation reactions, including Ferrier-type and Tsuji–Trost-type reactions, was finally enabled by an unprecedented, highly regioselective γ-deoxygenation of AR products by using Zn/HOAc and a diastereoselective Heck–Matsuda coupling. The synthetic utility of the reaction was demonstrated in the first asymmetric total synthesis of (−)-musellarins A–C and 12 analogues in 11–12 steps. The brevity and efficiency of our synthetic route permitted preparation of enantiomerically pure musellarins and analogues (>20 mg) for preliminary cytotoxicity evaluation, which led us to identify two analogues with three-to-six times greater potency than the musellarins as promising new leads.

Introduction

Achmatowicz rearrangement (AR) is a powerful transformation that can convert furfuryl alcohols (**I**) into, otherwise poorly accessible, fully functionalized dihydropyranone acetals (also known as pyranuloses; **I**→**II**, Figure 1) through an oxidative rearrangement process.[1] The synthetic utility[2] of AR products has been considerably expanded in recent decades by identification of new oxidants[3] (e.g., *meta*-chloroperbenzoic acid and *N*-bromosuccinimide) and the development of highly efficient transformations of dihydropyranone acetals (**II**), such as Kishi reduction[4] (**II**→**III**; Figure 1), Feringa-O'Doherty *O*-glycosylation[5] (**II**→**IV**; Figure 1), [5+2] cycloaddition[6] (**II**→**V**; Figure 1), and bicycloketalization[7] (**II**→**VI**; Figure 1). Exploiting these reactions as the key step provided efficient routes for the synthesis of complex natural products[2] and a library of skeletally diverse compounds for biological activity studies.[8] In particular, Kishi reduction has been widely recognized as the method of choice for the synthesis of functionalized *cis*-2,6-dihydropyranones (*cis*-DHPOs; **III**) due to the reproducibly high yield and predictable excellent *cis* diastereoselectivity (diastereomeric ratio (d.r.) > 20:1).[9] However, access to the corresponding *trans*-DHPOs from AR products has been rarely explored and, to the best of our knowledge, only two examples employing Ferrier-type alkynylation ($SnCl_4$, R≡CSiMe$_3$) or allylation (BF_3·Et_2O, allylsilane) were reported by Srihari and Sridhar[10] The closely related *trans* arylation leading to *trans*-DHPOs (**II**→**VII**; Figure 1) remains unknown. Herein, we disclose an effi-

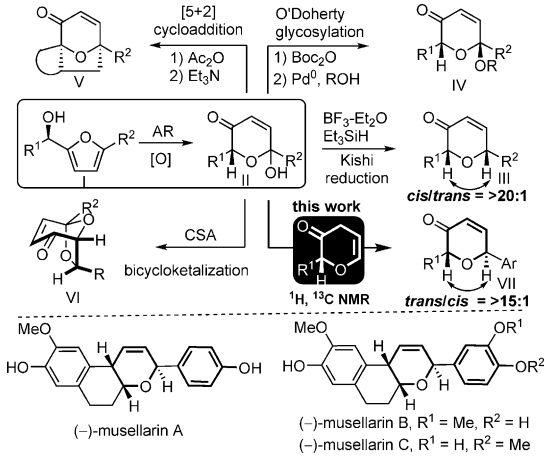

Figure 1. Selected key transformations of AR products and structures of the diarylheptanoids musellarin A–C. Ac = CH_3CO, Boc = *tert*-butoxycarbonyl, AR = Achmatowicz rearrangement, CSA = camphor sulfonic acid.

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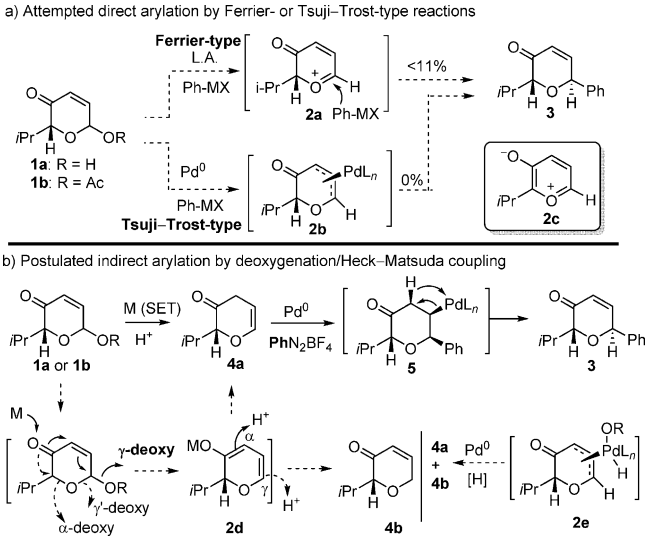
cient method that led to the first arylation of AR rearrangement products (**II**) with excellent 2,6-*trans* diastereoselectivity by an unprecedented regioselective reductive γ-deoxygenation and Heck–Matsuda coupling. The efficiency and utility of this new *trans* arylation were demonstrated in the first asymmetric total synthesis of the cytotoxic (−)-musellarins A–C[11] (Figure 1) and twelve analogues in only seven steps from furfuryl alcohol derivatives of type **I**.

Initially, we attempted direct arylation of pyranuloses **1a** and **1b** by a Ferrier-type reaction[12] (e.g., via cyclic oxonium ion **2a**) or Tsuji–Trost-type allyl–aryl coupling[13] (e.g., via allylpalladium **2b**)[14] (Scheme 1a). After extensive examination of



Scheme 1. a) Attempted direct arylation of AR products and b) postulated indirect *trans* arylation. NBS = *N*-bromosuccinimide.

the various Lewis acids and palladium precatalysts along with different arylmetal nucleophiles (see the Supporting Information for the screening conditions), we were disappointed to find that only $PhB(OH)_2/BF_3{\cdot}Et_2O$ or $TiCl_4$/ArZnCl promoted the reaction and only gave 7–11% yield of **3**. We speculated that the unsuccessful arylation might be attributed to facile formation of the reactive oxidopyrylium ion **2c** through loss of water or acetic acid.[2a–c] The capricious reactivity of AR products under both acidic and basic conditions prompted us to explore an indirect arylation approach based on a reduction–oxidation process (Scheme 1b). Inspired by Schmidt's seminal work[15] on Heck–Matsuda[16] arylation of simple 6-substituted dihydropyran enol ethers with aryl diazonium salts for *trans*-selective synthesis of 2,6-disubstituted dihydropyrans, we envisioned that γ-deoxygenation of AR products with migration of the double bond coupled with Heck–Matsuda arylation might provide a viable solution for the synthesis of *trans*-2-aryl-6-alkyl DHPOs **VII** (e.g., **3**). Challenges in implementing this strategy from a mechanistic point of view include 1) chemo- and regioselective γ-deoxygenation versus possible α- and γ′-deoxygenation, and subsequent α-protonation versus potential γ-protonation that could produce the thermodynamically more-stable but undesired conjugate enone **4b** and 2) unprecedented Heck–Matsuda reaction of δ-keto cyclic enol ethers of type **4a**.

Results and Discussion

After preliminary studies of Pd-catalyzed reductive deoxygenation[17] of AR products that gave inseparable mixtures of **4a** and **4b**, among other compounds, presumably via intermediate **2e** (Scheme 1b), we concentrated our efforts on deoxygenation by single-electron transfer (SET) by taking advantage of the adjacent enone functionality (**1a**/**1b**→**4a**). As shown in Table 1, SmI_2 was first evaluated as the reducing agent because

Table 1. Selected conditions for regioselective γ-deoxygenation of AR products to **4a**.[a]

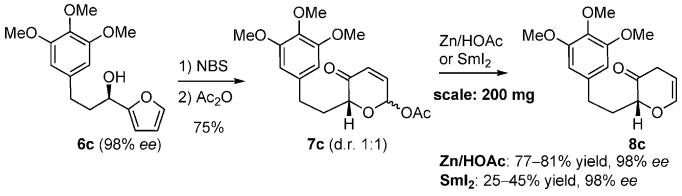
Entry	R	M (SET)	Solvent	Time	Yield[b] [%]
1	H (**1a**)	SmI_2	THF/H_2O (60:1)	10 min	<5
2	**Ac (1b)**	**SmI_2**	**THF/H_2O (60:1)**	**10 min**	**82**
3	Piv	SmI_2	THF/H_2O (60:1)	10 min	42
4	Boc	SmI_2	THF/H_2O (60:1)	10 min	0
5	Ac (**1b**)	SmI_2	THF/MeOH (10:1)	10 min	35
6	Ac (**1b**)	SmI_2	THF/*i*PrOH (20:1)	10 min	26
7	Ac (**1b**)	Mg	MeOH	1.5 h	0
8	Ac (**1b**)	Mg	HOAc	48 h	10
9	Ac (**1b**)	Fe	HOAc	48 h	49
10	**Ac (1b)**	**Zn**	**HOAc**	**1.5 h**	**81**
11	H (**1a**)	Zn	HOAc	1.5 h	23
12	Piv	Zn	HOAc	3 h	72
13	Boc	Zn	HOAc	3 h	68
14	Ac (**1b**)	Zn	CH_2Cl_2	11 h	60
15	Ac(**1b**)	Zn	MeOH	9 h	0
16	H (**1a**)	Zn	CH_2Cl_2	8 h	48

[a] The reaction was performed with AR products **1a**, **1b**, or derivatives (20 mg). [b] Isolated yield of **4a**. Piv = pivaloyl.

it has been used in a number of efficient reductive deoxygenation reactions.[18] Pleasingly, we found that SmI_2 (2.4 equiv) could efficiently reduce **1b** at 0 °C within 10 min to provide the deoxygenation product **4a** in 82% yield as the exclusive regioisomer (Table 1, entry 2) presumably through chemoselective γ-deoxygenation followed by regioselective α-protonation of **2d**, whereas under identical conditions **1a** gave a complex mixture (Table 1, entry 1). Notably, γ-protonation of **2d** leading to **4b** did not occur, which could not be rationalized at this stage without further experimentation. In addition, it was surprising that **4a** was stable to routine aqueous workup and column chromatography on silica gel and did not isomerize to the conjugate enone **4b**, which permitted full spectroscopic characterization of the product. Further screening of the reaction conditions revealed that the efficiency of the γ-deoxygenation was highly dependent on the leaving group (Table 1, entries 3 and 4), solvent (Table 1, entries 5 and 6), and the SET reagent (Table 1, entries 7–9). Unexpectedly, during these screenings we identified Zn (activated powder) in acetic acid as a new, cheap, and competent system for the regioselective γ-deoxygenation (Table 1, entry 10).[19] In particular, the strict

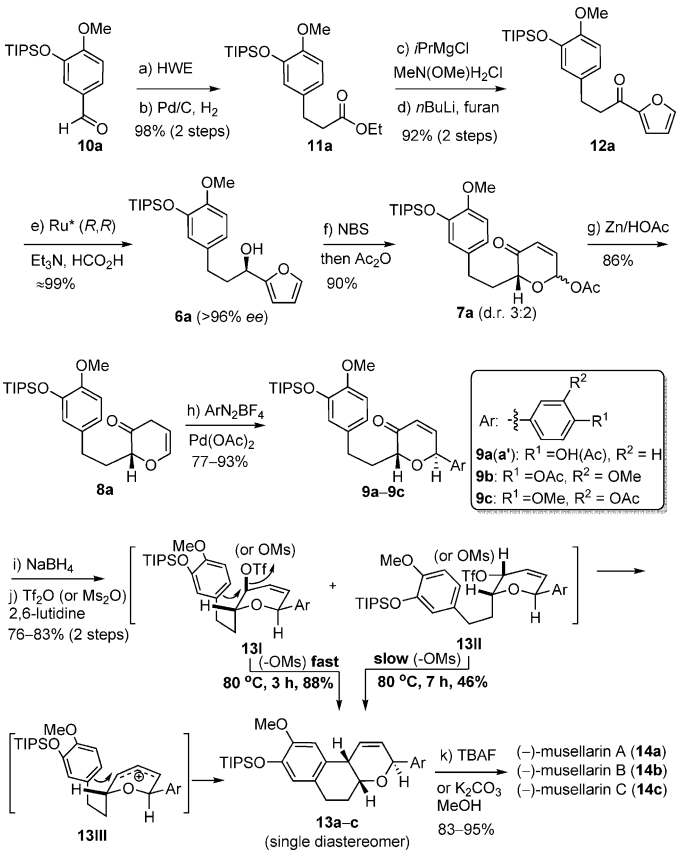
exclusion of oxygen from the reaction vessel required for the SmI_2 reaction was not necessary, which made the Zn reagent an attractive and practical alternative. It was noted that the deoxygenation efficiency was solvent dependent (Table 1, entries 10 and 11 versus 14–16) and that the SET metal (Table 1, entries 8–10) had more influence on the yield than the leaving group (Table 1, entries 10–13).

To further evaluate the efficiency and reproducibility of these two systems (SmI_2 versus Zn/HOAc) on a synthetically useful scale (200 mg to 1.0 g) and to determine whether racemization occurs, we carried out AR of optically active substrate **6c** (98% enantiomeric excess (*ee*); see Scheme 3 below for preparation of **6c**), then acetylation, and γ-deoxygenation (Scheme 2). The γ-deoxygenation yield after reaction with SmI_2 on a 200 mg scale dropped significantly to 25–45% (repeated three times), even though no racemization was observed. In contrast, Zn/HOAc gave a consistently high yield (77–81%) of **8c** on a 200 mg, 500 mg, and 1.0 g scale without epimerization (98% *ee*, repeated three times, the *ee* value of each run was determined by chiral HPLC). These findings clearly suggested that Zn/HOAc was the method of choice for large-scale γ-deoxygenation of AR products, especially with the additional advantages, which included easy operation (rt, no exclusion of oxygen), low cost, and readily available reagents.



Scheme 2. Comparison of γ-deoxygenation with Zn/HOAc and SmI_2 on a 200 mg scale with enantiomerically pure substrate. TIPS = triisopropylsilyl, Tf = triflyl, Ms = mesityl, TBAF = tetrabutylammonium fluoride.

With the optimal γ-deoxygenation conditions in hand, we explored the Heck–Matsuda coupling of **4a** with aryl diazonium salts postulated in Scheme 1b. Gratifyingly, after preliminary investigation of the palladium catalyst and solvent palladium tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was found to rapidly catalyze the coupling of **4a** with PhN_2BF_4 in acetonitrile at rt to give *trans*-2,6-DHPO **3** in 88% yield as a single diastereomer (d.r. ≥ 20:1, based on ^1H NMR spectroscopy of the crude reaction mixture). Subsequently, we found that $Pd(OAc)_2$ was a more-effective and general precatalyst for electron-rich aryl diazonium salts such as (4-MeO)PhN_2BF_4. The 2,6-*trans*-diastereoselectivity was further confirmed by NOE experiments (see the Supporting Information). Notably, the δ-carbonyl group of the dihydropyran **4a** did not provoke any problems for the Heck–Matsuda coupling but facilitated β-hydride elimination (**5**→**3**, Scheme 1b) to form the corresponding thermodynamically favorable conjugate enone, which would not undergo Pd-catalyzed migratory olefin isomerization through the well-known hydridopalladium addition/elimination sequence.[20] This exciting result prompted us to initiate the asymmetric total synthesis of musellarins A–C (Scheme 3)[21] by exploiting Zn-mediated γ-deoxygenation and Heck–Matsuda coupling.



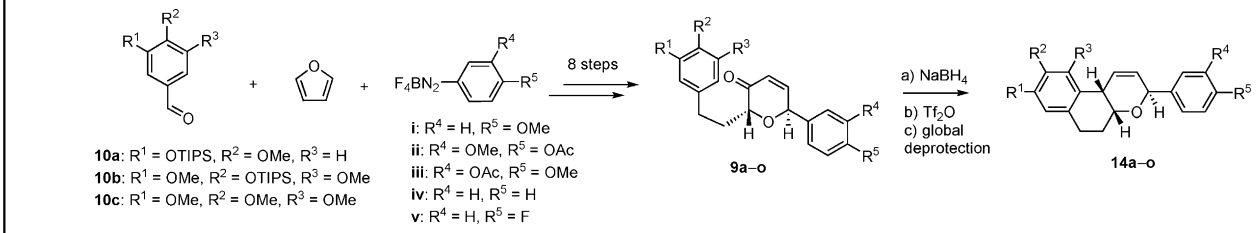
Scheme 3. Asymmetric total syntheses of (−)-musellarins A–C.

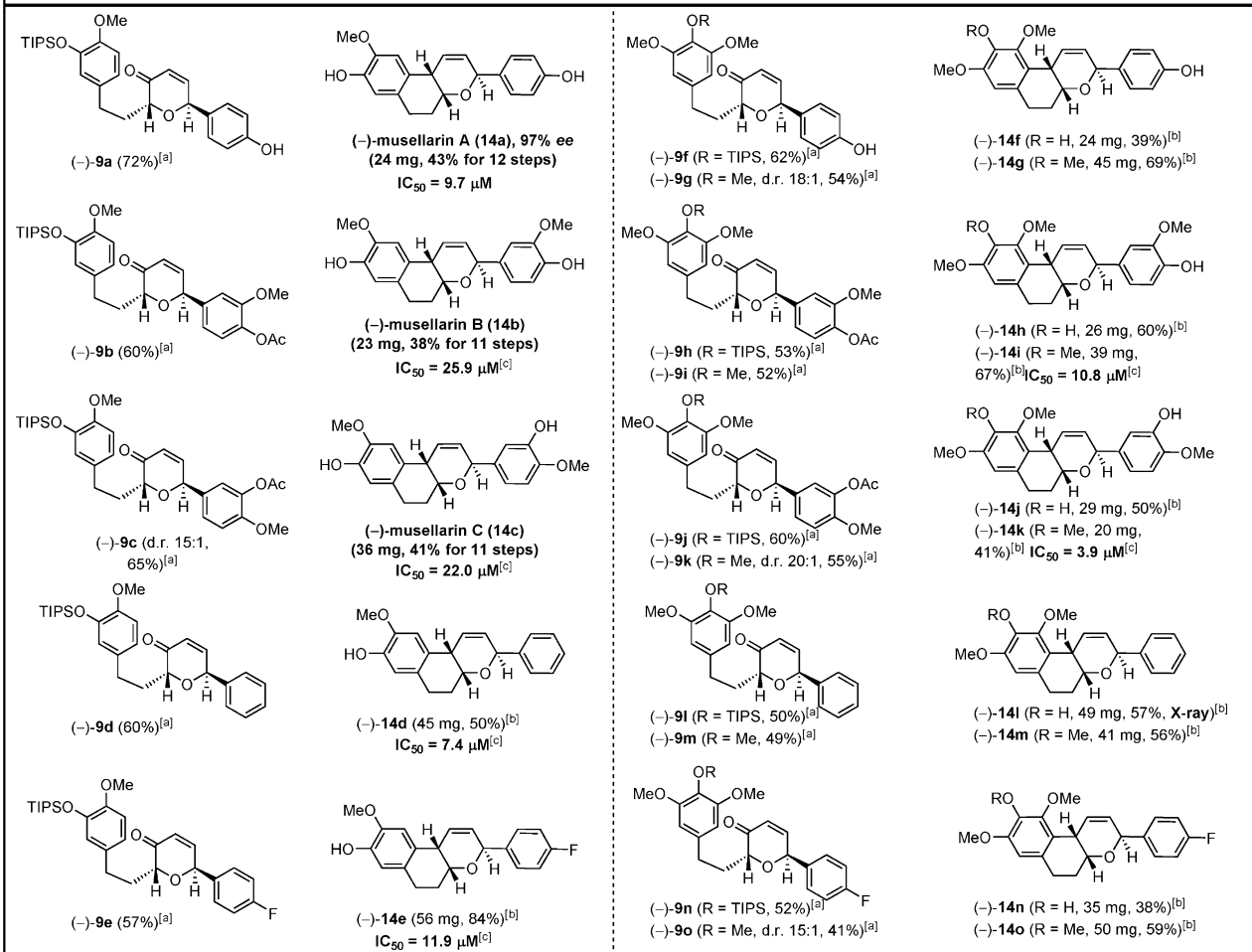
Our synthesis (Scheme 3) began with the preparation of enantiomerically pure furfuryl alcohol **6a**, which was obtained in 89% yield from aldehyde **10a** through a straightforward five-step sequence: Horner–Wadsworth–Emmons (HWE) olefination, Pd-catalyzed hydrogenation, Weinreb amide formation, lithiated furan addition, and Noyori asymmetric transfer hydrogenation (ATH).[22] AR of **6a** followed by acetylation provided substrate **7a** for the key γ-deoxygenation step, which proceeded smoothly under our optimized conditions (Zn/HOAc) to afford **8a** in 86% yield. Heck–Matsuda coupling of **8a** with one of three different aryl diazonium salts, corresponding to musellarins A–C, was catalyzed by $Pd(OAc)_2$ in acetonitrile at rt to give **9a–c** in excellent yield. Protection of the phenol group of **9a** as the acetate derivative (**9a'**) was required to minimize destructive interference in the subsequent intramolecular Friedel–Crafts reaction, one of the key steps in this new synthetic strategy. Chemoselective carbonyl reduction of **9a'** and **9b–c** with $NaBH_4$ (or $CeCl_3$-$NaBH_4$, diisobutylaluminum hydride, or $LiBEt_3H$) gave a 1:1 to 1:4 diastereomeric mixture of secondary alcohols that was subjected to triflic anhydride-promoted intramolecular Friedel–Crafts[23] cyclization at −78 °C for 4 h to provide the tetracyclic compounds **13a–c** as single diastereomers in excellent overall yield over two steps. Careful monitoring of the reaction progress by TLC suggested that one diastereomer

underwent rapid Friedel–Crafts cyclization (< 0.5 h), whereas the other was slowly consumed (3–4 h at −78 °C). Interestingly, individual subjection of these two diastereomeric alcohols to mesylation for the Friedel–Crafts cyclization revealed that the *trans* isomer (**13 I**) gave 88% yield after 3 h at 80 °C, whereas the *cis* isomer (**13 II**) afforded only 46% yield after 7 h under identical conditions, along with significant decomposition (Ar was 4-acetoxyphenyl, 3-methoxy-4-acetoxyphenyl, or 3-acetoxyl-4-methoxyphenyl. These findings implied that reaction of the *cis* isomer (**13 II**) might involve a S_N1-type mechanism (via a carbocation such as **13 III**) and an S_N2-type pathway might operate for the *trans* isomer (**13 I**). Although more work is necessary to fully elucidate a detailed mechanism, we chose to move forward. Global deprotection of **13 a–c** furnished (−)-musellarins A–C in 83–95% yield. All spectroscopic data for our synthetic samples were in good agreement with those reported for the natural musellarins A–C.[24] The identical sign of the optical rotations of the synthetic and natural musellarins confirmed their absolute configurations.[24] This represents the first asymmetric total synthesis of cytotoxic diarylheptanoids (−)-musellarins A–C with 38–42% overall yield in 11–12 steps (longest linear sequence), which is much-more efficient than our previous synthesis (7.8–9.8% yield, 15–16 steps).

The remarkable brevity and efficiency of our synthetic route, enabled by the newly established reductive γ-deoxygenation and Heck–Matsuda reaction, was further demonstrated in the

Table 2. Examples of *trans*-2-aryl-6-alkyl DHPOs and their conversions to musellarins A–C and 12 analogues.





[a] Isolated yield from **6 a–c** over four steps. [b] Isolated yield from **9 a–o** over three/four steps. [c] IC_{50} [μM] was obtained in 48 h against HL60 by using oxaliplatin as the positive control (IC_{50} = 1.6 μM).

enantioselective synthesis of *trans*-2-aryl-6-alkyl DHPOs **9d–o** and 12 musellarin analogues **14d–o** (Table 2). Three different aromatic aldehydes (**10a–c**) and five readily available aryl diazonium salts (**i–v**)[21,24] were employed in our studies to showcase the efficiency and utility of the two-step *trans*-arylation method to access *trans*-DHPOs of type **VII**. A three/four step elaboration of *trans*-DHPOs **9a–o** produced 12 enantiomerically pure analogues **14d–o** with comparable overall yields (19–48% yield, 20–56 mg) to the above-described musellarins.

Because naturally occurring musellarin B (**14b**) was reported to be cytotoxic to several cancer cell lines with IC_{50} values ranging from 21.3 μM (HL-60) to >40 μM (MCF7)[11b] and musellarin A was shown to significantly induce quinone reductase (QR) activity (9.3 μM),[11a,25] we performed a preliminary evaluation of the cytotoxicity of **14a–o** against cancer cell lines HL60 (blood), HepG2 (liver), and MCF7 (breast) by using normal cells of primary cortical neurons (PCN) as a selectivity reference. As shown in Table 3, our synthetic musellarins were moderately active to HL60 but inactive to HepG2 and MCF7, consistent with the corresponding reported cytotoxicity of the natural musellarins. Notably, analogues **14d** and **14k** have a more-potent and selective in vitro antitumor activity against HL60 with IC_{50} values of 7.4 (selectivity index: 3.19) and 3.9 μM (selectivity index: 4.54), respectively,[24] whereas they are inactive (IC_{50} >40 μM) to HepG2 and MCF7.

Table 3. Cytotoxicity of musellarins A–C and selected analogues.[a]

Compound	PCN[b] IC_{50} [μM]	HL60 IC_{50} [μM]	HepG2 IC_{50} [μM]	MCF7 IC_{50} [M]
14a (musellarin A)	23.8	9.7	44.1	>50
14b (musellarin B)	65.3	25.9	>50	>50
14c (musellarin C)	>50	22.0	>50	>50
14d	23.6	**7.4**	>50	>50
14e	33.1	11.9	>50	>50
14i	29.6	10.8	>50	>50
14j	>50	23.1	46.1	>50
14k	17.7	**3.9**	40.4	>50
oxaliplatin[c]	N/A[d]	1.56	5.28	12.99

[a] IC_{50} [μM] was obtained in 48 h. [b] PCN = primary cortical neurons. [c] Oxaliplatin was used as the positive control [μM]. [d] Not applicable.

Conclusion

We have developed a highly regio- and diastereoselective *trans* arylation of AR products by an unprecedented Zn-mediated reductive γ-deoxygenation and Heck–Matsuda reaction, leading to a novel, efficient, and stereoselective synthesis of *trans*-2-aryl-6-alkyl DHPOs. The synthetic utility of this new *trans*-arylation method was demonstrated in the first asymmetric total synthesis of (−)-musellarins A–C and 12 analogues. Importantly, this protocol can greatly expand the utility of AR in the synthesis of tetrahydropyran-containing natural products and might be exploited for stereoselective C-aryl glycosylation.[26] Finally, preliminary cytotoxicity evaluation of the tetracyclic diarylheptanoids synthesized allowed us to identify analogues **14d** and **14k** as promising antitumor lead compounds selective against HL60.

Experimental Section

Deoxygenation

Method a: Compound **1b** (0.11 g, 0.51 mmol) dissolved in THF/H_2O (6.0:0.1 mL) was added to a stirred solution of SmI_2 (0.1 M in THF, 11.6 mL, 1.16 mmol) in a round-bottomed flask at 0 °C. The reaction mixture was stirred for 10 min, then the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3×5 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford **4a** (133 mg, 0.95 mmol, 82%) as a colorless oil.

Method b: Activated Zn powder (0.16 g, 2.53 mmol) was added to a stirred solution of **1b** (0.11 g, 0.51 mmol) in acetic acid (5 mL) at rt. The reaction mixture was stirred for 1.5 h. The reaction was quenched by addition of a saturated aqueous solution of K_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3×5 mL). Workup and purification as described for method a gave **4a** (132 mg, 0.94 mmol, 81%).

Heck–Matsuda Coupling

Phenyldiazonium tetrafluoroborate (53.1 mg, 0.27 mmol), NaOAc (56 mg, 0.69 mmol), and $Pd_2(dba)_3$ (16.8 mg, 18.1 μmol) were added to a stirred solution of **4a** (32.1 mg, 0.23 mmol) in CH_3CN (3 mL) at rt. The reaction mixture was stirred for 3 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3×5 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to afford **3** (43.8 mg, 0.20 mmol, 88%) as a reddish oil.

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Keywords: Achmatowicz rearrangement · arylation · musellarins · total synthesis · zinc

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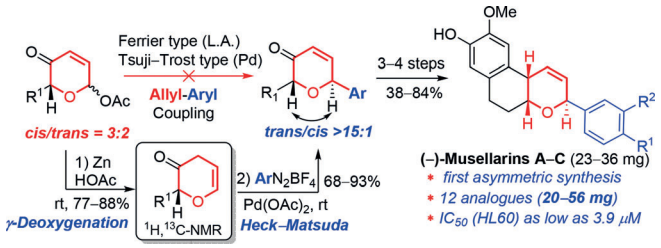

O leaves, Ar comes: A highly regio- and diastereoselective *trans*-arylation of Achmatowicz rearrangement products by an unprecedented Zn-mediated reductive γ-deoxygenation and Heck–Matsuda reaction was developed for the efficient synthesis of *trans*-2-aryl-6-alkyl dihydropyranones (see scheme). The synthetic utility of this new method was further demonstrated in the first asymmetric total synthesis of (−)-musellarins A–C and 12 analogues in 11–12 steps.

Synthetic Methods

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Highly *trans*-Selective Arylation of Achmatowicz Rearrangement Products by Reductive γ-Deoxygenation and Heck–Matsuda Reaction: Asymmetric Total Synthesis of (−)-Musellarins A–C and Their Analogues