Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000424

Link to VoR: <https://doi.org/10.1002/ejoc.202000424>

Expedient Pd-Catalyzed α -Arylation Route to Dibenzoxepinones. Pivotal Manske's Ketone for the Formal Synthesis of Cularine Alkaloids

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In Memoriam Richard H. F. Manske, an outstanding alkaloid chemist who also demanded excellence in scientific verse.

Abstract: The general synthesis of diversely substituted dibenzoxepinones by a combined Pd-catalyzed α -arylation and S_NAr strategy is reported and applied to the synthesis of Manske's ketone, a key intermediate en route to the total synthesis of four cularine alkaloids. In the course of this work, an unanticipated ring contraction reaction to a xanthone was observed and serves as a caveat for the conditions of the widely used α -arylation reaction.

In his systematic, life-long study of benzyl isoquinoline alkaloids, Manske discovered the structurally unusual family of bioactive cularines^[1-4] (Figure 1, A). Since its original isolation in 1938,^[5] cularine (**1**) and its congeners have suffered a scarcity of isolated material^[5,6] due to limitations of plant extraction strategies which, together with their bioactivity, served as inspiration to the synthetic community. In pioneering studies, Manske proposed 10,11-dihydro-2,3,4-trimethoxydibenz[*b,f*]oxepin-10-one (**2**, Figure 1, A) as a key intermediate for the synthesis of cularine. However, his classical Friedel-Crafts approach, afforded low yield (1%) of **2** leaving "little hope for the synthesis of cularine by this method".^[7] It was not until 1963 that Kametani and Fukumoto prepared sufficient quantities of Manske's ketone (**2**) to allow the first total synthesis of cularine.^[8] Given the harsh conditions required to forge the dibenzoxepine core, demands for an alternative strategy were met by Domínguez, who developed an effective but lengthy route to **2** using dithiane alkylation and Ullmann coupling as key steps.^[9] Their subsequent elaboration of this key intermediate provided access to the full spectrum of cularine alkaloids, including cularine itself, cularimine, oxocularine, and dioxocularine,^[10] as well as the non-natural O-methylmimosamine^[10] and aristocularine.^[11] In concurrent biomimetic approaches to the cularines,^[12] intermediates in the synthesis of crassifoline were shown to undergo 7-membered ring formation either through oxidative coupling,^[12a] Ullmann condensation,^[12b] or nucleophilic substitution.^[12c] Although elegant, such strategies necessitate early-stage installation of the N-heterocycle thereby limiting the range of accessible Cularines.

Figure 1. A) The cularine alkaloids and Manske's ketone **2**, the key synthetic intermediate. B) Previous synthetic strategies to 10,11-dihydrodibenz[*b,f*]oxepin-10-ones and biologically active dibenzoxepine containing compounds. C) Retrosynthetic analysis for dibenzoxepinones **3**.

Aside from approaches developed during the synthesis of the cularine alkaloids, the classical Friedel-Crafts acylation, a reaction suffering from harsh reaction conditions (e.g. up to 4 equiv $AlCl_3$ at rt or excess PPA at 100 °C), constitutes the dominant tactic for the construction of 10,11-dihydrodibenz[*b,f*]oxepin-10-ones.^[13] Although a lateral metalation reaction has shown utility for the synthesis of the N-heteroatom related dibenzo[*b,f*]azepinones, its application to the corresponding 10,11-dihydrodibenz[*b,f*]oxepin-10-ones has met with limited success.^[14] More recently, a report by Rossi employs an intriguing photochemical method to construct benzo-fused heterocycles; however, the scope of this reaction for dibenzoxepinones is restricted to a single example.^[15]

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Supporting information for this article is given via a link at the end of the document.

Table 1. Scope of 2'-fluoroacetophenones **7** in the Synthesis of Dibenzoxepinones **10**

Entry	S _N Ar Product ^a	α-Arylation Product ^a	Entry	S _N Ar Product ^a	α-Arylation Product ^a	Entry	S _N Ar Product ^a	α-Arylation Product ^a
1			9			17		
2			10			18		
3			11			19		
4			12			20		
5			13			21		
6			14			22		
7			15			23		
8			16			24		

^aYields of isolated products; for **10**, yields in parenthesis obtained using PdCl₂(PPh₃)₂ (10 mol%), PPh₃ (30 mol%), Cs₂CO₃ (3 equiv), PhMe, reflux, 16-20h.

^bReaction performed at 140 °C for 196 h. ^cReaction performed at 140 °C for 70 h. ^dReaction performed at 100 °C for 40 h. ^eReaction using 5-10mol% Pd₂(dba)₃/XantPhos. ^f1-(7,8-dimethoxydibenzo[b,d]furan-4-yl)ethan-1-one was isolated in 33% yield, see SI. ^gPrepared via Ullmann condensation, see SI.

Mindful of the limitations of the previous approaches to Manske's ketone (**2**) and inspired by the diversity of Cularine natural products accessible from this pivotal intermediate, we sought to develop a more efficient route to this ubiquitous heterocycle which is also prevalent in medicinal agents (Figure 1, B). We envisaged two key sequential disconnections to dibenzoxepinones **3** (Figure 1, C): intramolecular palladium-catalyzed α-arylation^[16] to effect oxepine ring closure and C–O bond formation to furnish intermediate diaryl ether **4** by an S_NAr reaction between the readily available 2'-fluoroacetophenones (**5**) and 2-bromophenols (**6**). Herein we report a general synthesis of dibenzoxepinones and the application of this

method to the construction of Manske's ketone (**2**), the pivotal late-stage intermediate for four Cularine alkaloids.^[17]

To initiate the study, the intramolecular α-arylation of diaryl ether **9a**, prepared from S_NAr reaction of 2-fluoroacetophenone (**7a**) with 2-bromophenol (**8a**), to the prototype dibenzoxepinone **10a** was examined (Table 1, entry 1). The cyclization was initially carried out using a catalyst system comprising PdCl₂(PPh₃)₂ (5 mol%)/PPh₃ (30 mol%), which delivered the desired product in 61% yield. Considerable further optimization studies in catalyst loading, solvent, and temperature (see SI) demonstrated that a 1:1 ratio of Pd to XantPhos(5mol%), Cs₂CO₃ as base, and toluene as solvent is optimal for the

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process, giving **10a** in 72% yield. The reaction also proceeded to completion when run at 80 °C and the catalyst loading could be decreased to 0.625 mol% before starting material consumption was significantly affected. Control experiments performed in the absence of both Pd₂(dba)₃ and ligand led to complete recovery of starting material **9a**.

The scope of the new methodology with respect to substitution on the acetophenone ring was next explored. For this purpose, diaryl ethers **9b-i** were prepared via S_NAr chemistry between variously substituted 2'-fluoroacetophenones **7b-l** and 2-bromophenol **8a** (Table 1, entries 2-9). When compounds **9b-i** were subjected to the standard α -arylation conditions, the corresponding dibenzoxepinones **10b-h** were obtained in good yields. Weakly electron withdrawing groups (EDGs) and electron donating groups (EWGs) *meta* (entries 2 and 3) and strongly EWGs *para* or *ortho* to the ketone (entries 4 and 5) were well tolerated. However, the chloroacetophenone **9f** afforded the corresponding dibenzoxepinone **10f** in only 34% yield. The role of electronics on the reactivity of the acetophenone moiety is emphasized by the slightly lower yields observed when strong EDGs were *para* or *meta* to the ketone (entries 7 and 8). An incomplete conversion to **10g** and **10h** was observed after 15 h. However, increasing the reaction time to 40 h led to synthetically useful yields of 59% and 63% respectively. When the rates of the intramolecular α -arylation step for **9a**, **9d**, and **9g** were compared, full conversion of *para*-trifluoromethyl-containing substrate **9d** to **10d** was observed after 8 h while conversion to the 7-methoxy-substituted dibenzoxepinone **10g** required 40 h, considerably longer than that needed for the unsubstituted substrate **9a** (15 h).^[18] Unfortunately, no conversion of the acyl pyridine **9i** was detected under the reaction conditions.

We next turned our attention to variation of the phenol partner in the S_NAr and intramolecular α -arylation sequence and the reaction of differentially substituted 2-bromophenols **8** with 2'-fluoroacetophenone **7a** to give products **10j-r** was established (Table 1, entries 10 to 18). Sterically encumbered phenol **9j** (entry 10) as well as corresponding substrates bearing a weakly EDG (entry 12), halogen (entries 13 and 14), or strongly EDG (entry 15) were well tolerated. An EWG *para* to the bromo substituent (entry 16) performed significantly better than an EDG (entry 15). 2-Naphthol derived substrate **9r** also performed well to give the benzonaphthoxepinone **10r** (entry 18). Much like the reactivity observed for **9i**, the α -arylation of heterocycle-derived substrate **9s** (entry 19) afforded **10s** in low yield. Looking to

expand the scope to other heterocyclic systems, diaryl thioether **9t** was prepared and exposed to the optimized α -arylation conditions (Table 1, entry 20). Unfortunately, the reaction proved sluggish, with **10t** being isolated in only 32% after 40 h reaction time and with increased catalyst loading (5 mol% Pd₂(dba)₃/10 mol% XantPhos). Substrate **9u**, prepared via Ullmann condensation of 2'-iodoacetophenone with 2-bromo-*N*-methylaniline, failed to deliver dibenzazepinone **10u** (Table 1, entry 21).

The reaction scope was also successfully expanded to provide 11-substituted dibenzoxepinones **10v-x** (Table 1, entries 22-24). Thus, diaryl ethers **9v-x**, prepared via S_NAr, addition of the appropriate Grignard reagent to 2-(2-bromophenoxy)benzonitrile, or by alkylation of **9a** (see SI), were subjected to the standard α -arylation conditions to afford products **10v-x** in 39-85% yields.

Further manipulation of **10a/10l** highlights the utility of the dibenzoxepinone products (Scheme 1). Thus, Suzuki-Miyaura coupling of **10l** with 3-methoxyphenylboronic acid and C-N coupling with morpholine both proceeded smoothly to give biaryl **11a** and tertiary amine **11b** in 90% and 61% yields, respectively. Alkylation of **10a** with ethyl chloroformate gave an excellent yield of β -keto ester **11c** that provides an opportunity for further functional group transformation. Furthermore, ketone **10a** was subjected to a sequence of triflation and Suzuki-Miyaura coupling to afford **11d** in 73% yield over two steps.

Scheme 1. Selective chemistry of dibenzoxepinones. (a) **10l** (0.50 mmol), 3-methoxyphenylboronic acid (1.5 equiv), Pd(OAc)₂ (2.5 mol%), SPhos (10 mol%), K₂CO₃ (3.0 equiv), MeCN (0.4 M), 100 °C 4 h; (b) **10l** (0.25 mmol), morpholine (1.2 equiv), Pd(OAc)₂ (2 mol%), JohnPhos (4 mol%), NaOtBu (1.4 equiv), 110 °C, 20 h; (c) **10a** (0.48 mmol), NaH (2.0 equiv), ClCO₂Et (3.0 equiv), THF, rt, 18 h; (d) 1. **10a** (0.24 mmol), Tf₂O (2.0 equiv), DIPEA (3.5 equiv), CH₂Cl₂, rt, 24 h, 78%; 2. 3-methoxyphenylboronic acid (1.5 equiv), Pd(PPh₃)₄ (10 mol%), 2M aq. Na₂CO₃ (5.0 equiv), DME, 90 °C, 18 h, 94%.

Scheme 2. Synthesis of Manske's ketone **2** via precursor **13**. ^a46% yield of isolated **18** when aqueous work-up was avoided.

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Having successfully established the scope of the new methodology for the construction of dibenz[b,f]oxepin-10-ones, attention turned to the original goal –Manske's ketone (**2**), the key intermediate for the synthesis of the cularine alkaloids. In contrast to the general S_NAr protocol established above, the reaction of 2-fluoro-3-methoxyacetophenone (**7h**) with 2-bromo-4,5-dimethoxyphenol failed to deliver the requisite intermediate **13** (Scheme 2). The problem was circumvented by devising two effective synthetic routes. Thus, S_NAr of acetophenone **7h** with 3,4-dimethoxyphenol followed by bromination afforded diarylether **13** (70% overall yield); alternatively, treatment of 2-fluoro-3-methoxybenzonitrile **14** with 2-bromo-4,5-dimethoxyphenol furnished diaryl ether **15** which, upon sequential bromination and MeMgBr treatment, delivered **13** (65% overall yield).

Exposure of diaryl ether **13** to our initial conditions used in the intramolecular α -arylation reaction ($PdCl_2(PPh_3)_2/PPh_3$) did not yield the anticipated Manske's ketone **2** but, unexpectedly, afforded the xanthone **17** as the sole product in low yield (Scheme 2).^[19] However, exposure of diaryl ether **13** to our general intramolecular α -arylation conditions furnished, gratifyingly, Manske's ketone **2** in 69% yield. Our synthesis of Manske's ketone in overall yields of 48% (3 steps from **7h**) and 45% (4 steps from **14**) may be favourably compared to those of Manske^[7] (2 steps, 1% yield) and Domínguez^[10] (5 steps, 18% yield) and its pivotal position in the synthesis of several Cularine alkaloids (e.g. cularine, cularimine, oxocularine, and dioxocularine) is well documented.^[10]

In order to shed light on the mechanism of the ring contraction reaction to xanthone derivative **17**, similar to an observed intermolecular reaction,^[20] we noted the reported oxygen- and light-promoted oxidative cleavage of exocyclic xanthene to xanthone^[21] and undertook reaction monitoring under the $PdCl_2(PPh_3)_2/PPh_3/K_3PO_4$ conditions by ¹H NMR analysis of the reaction mass at regular time intervals (see SI). Upon complete consumption of **13**, the reaction mixture was subjected to column purification (avoiding the aqueous work-up) to afford the xanthene **18** and xanthone **17** in 46% and 3% yields, respectively. Furthermore, we found (for ¹H NMR study, see SI) that the isolated xanthene **18** was readily converted to xanthone **17** and that the rate of conversion was accelerated by exposure to oxygen (Scheme 2), in accordance with previous studies of similarly substituted xanthenes.^[22] This observation clarifies the source of the xanthone **17** product.

In conclusion, we have demonstrated a new combined S_NAr/α -arylation sequence for the synthesis of dibenz[b,f]oxepinones. Following a diversion which led unexpectedly led to the xanthone **17**, the main goal of the devised two-step strategy, the synthesis of Manske's ketone (**2**), was achieved, constituting the most efficient synthesis to date of this pivotal intermediate for the assemblage of the Cularine alkaloids. The present work constitutes the formal synthesis of four alkaloids (Cularine, Cularimine, Oxocularine, and Dioxocularine). Our efficient and abbreviated route to the dibenzoxepinones, which also represent a structural feature of a number of bioactive molecules (Figure 1, B), may elicit further application of our synthetic strategy.

Acknowledgements

We acknowledge NSERC Canada for consistent support to our synthetic programs via the Discovery Grant (DG) program. We are grateful to Drs. Françoise Sauriol and Gabriele Schatte (Department of Chemistry, Queen's University) for their expert assistance on NMR spectroscopy and X-ray crystallography respectively.

Keywords: dibenz[b,f]oxepin-10-ones • alkaloids • Palladium • α -arylation • Manske's ketone

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Entry for the Table of Contents

Layout 2:

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Page No. – Page No.

**Expedient Pd-Catalyzed α -Arylation
Route to Dibenzoxepinones. Pivotal
Manske's Ketone for the Formal
Synthesis of four Cularine Alkaloids**

We report on the intramolecular Pd catalysed α -arylation→cyclization sequence for the synthesis of dibenz[b,f]oxepin-10-ones **10** from diarylethers **9**. Extensive substrate scope was investigated varying substitution pattern on both the rings of **9**. The present work demonstrates the shortest route to Manske's ketone **2**, a pivotal intermediate for the synthesis of four of the Cularine alkaloids.

Key Topic: Pd-catalysis, Alkaloid Synthesis