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Domino Reactions for the Synthesis of Anthrapyran-2-ones and the Total Synthesis of the Natural Product (±)-BE-26554A

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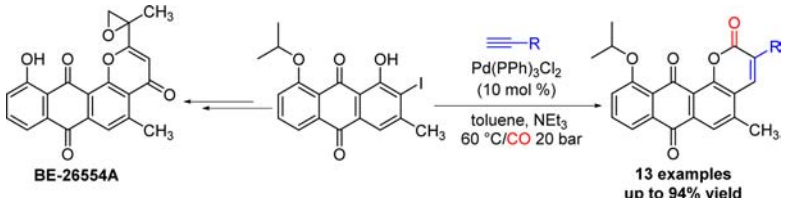
ABSTRACT



A domino alkyne addition/CO insertion/Nu acylation reaction to a series of novel anthrapyran-2-ones in good to excellent yields is described. In addition, an efficient synthetic sequence involving carbonylation, formation of a β-keto-sulfoxide, and cyclization is presented en route to the antibiotic and antitumor compound (±)-BE-26554A.

Domino reactions have provided more efficient methods for the synthesis of a range of complex ring systems in industry and academia.[1] The discovery and optimization of domino reactions also provides efficient access to a variety of new compounds, sometimes having interesting pharmacological properties.[2,3] In this regard, the structural class of anthrapyranones have a remarkable range of biological activity mainly as antibacterial agents or antitumor compounds. Some examples in this family of compounds are pluramycin A, kidamycin, and the antibiotic saptomycin E.[4,5] In 1994, the related compound BE-26554A (**1**)[6] has been isolated from *Streptomyces A26554* cultures by the Banyu Pharma group. This anthrapyran-4-one and the C2-functionalized analogues have an excellent range of IC_{50} values of 0.017−0.0007 μM in P388 leukemia cells. Given this evaluation of **1** and its derivatives, these compounds provide excellent synthetic targets to enable further biological evaluation.

The synthesis of natural product anthrapyranones has seen several different approaches from various groups.[7] Originally, we conceived the application of a domino CO insertion/Sonogashira/6-*exo*-*dig* cyclization of aryl halides as a possible alternative, offering a rapid approach to the construction of the D-ring found in such natural products. This approach has been used for the production of various heterocycles[8] including chromones as well as flavones

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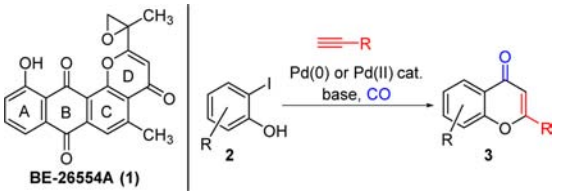
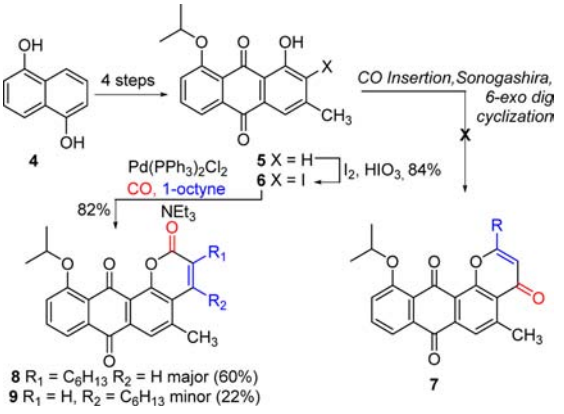
Scheme 1. BE-26554A (**1**) and a Domino CO Insertion/Sonogashira/6-*Exo*-*Dig* Cyclization to Chromones and Flavones



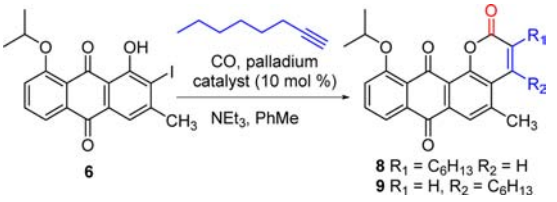
(Scheme 1, **2** to **3**).[9] For our purposes, previously established carbonylative Sonogashira reaction conditions could be used as a guide for more complicated substrates.[9d] In this context, CO insertion into a Pd−aryl bond was found to be challenging in a sterically hindered *ortho*,*ortho*-disubstituted position.[10] For the application of this domino reaction we required the halogenated anthraquinone **6**, where methodology, described earlier for the protonated variant **5**, was available (Scheme 2).[11,7a] Iodination of **5**, using iodic acid and iodine, furnished the domino precursor aryl iodide **6** in excellent yield (84%).

Scheme 2. Domino CO Insertion Reaction Resulting in Isomers **8** and **9**



Unlike the previously discussed work preparing the simpler chromones,[9] but similar to the early carbonylative cross coupling work in the anthraquinone series of the Martin group,[7b] under standard conditions we were also unable to produce the anthrapyran-4-one ring system **7**. However, when 1-octyne and aryl iodide **6** were reacted the anthrapyran-2-one ring regioisomers **8** and **9** were isolated in excellent yields (82%), signifying a late-stage carbonylation process.[12] In rare instances (and often with lower yields/different regioselectivity), such reactions have been demonstrated in the formation of simpler coumarins with terminal alkynes.[13,14] Reactions with internal alkynes have been reported by Larock, suggesting a similar type of mechanism.[15] In order to optimize the conditions for the production of **8** and **9** we carried out a series of reactions under various catalytic conditions (Table 1).

Table 1. Methodological Development of Domino Alkyne Insertion/Carbonylation/Nu-Acylation Reaction



entry	catalytic conditions	temp (°C)/CO pressure (bar)	yield (%) (ratio **8**:**9**)
1	$Pd(PPh_3)_2Cl_2$	60/20	82 (2.7:1)
2	$Pd(PPh_3)_2Cl_2$	60/60	53 (2:1)
3	$Pd(PPh_3)_2Cl_2$, CuI	60/20	0[a]
4	$Pd(PPh_3)_2Cl_2$ (5:1 dioxane/H_2O)	60/20	0
5	$Pd(PPh_3)_2Cl_2$	60/1	67 (6.4:1)
6	$Pd_2(dba)_3 \cdot CHCl_3$, Xantphos	60/20	0[a]
7	$Pd_2(dba)_3 \cdot CHCl_3$, *t*-Bu_3P	60/20	30
8	$Pd_2(dba)_3 \cdot CHCl_3$, XPhos	60/20	43[b]
9	$Pd(OAc)_2$, Ad_2Pn-Bu	60/20	0[a]
10	PEPPSI-*i*Pr	60/20	28 (2.5:1)[b]
11	$Pd(dppf)Cl_2$	60/20	NR
12	[(cinnamyl)PdCl]$_2$	60/20	NR

[a] Reaction resulted in complex mixture of products. [b] In each of these cases a large amount of product resulting from protonation of **6** resulted.

Modifications of the $Pd(PPh)_3Cl_2$-catalyzed reaction, such as changing the solvent system and using a copper additive, were less effective. Interestingly, increasing the pressure of CO (entry 2) still resulted in production of the 2-pyranone derivatives, but in a lower yield, while a decrease of pressure dramatically improved the regioselectivity (ca. 6:1 for **8**:**9**, entry 5). We propose that an alkyne Pd precomplexation equilibrium process at lower pressures is a dominant factor in this result. In order to produce intermediates with more electron density on the palladium, the electron-rich phosphine systems (entries 6−9) were tested. However, these were also less efficient; the back-donation to the carbonyl ligand possibly slowed down the initial CO insertion step.[16] Pd(dppf), [(cinnamyl)PdCl]$_2$, and the bis-adamantyl *n*-butyl phosphine (cataCXium,[17,18] all failed to deliver any pyranone ring containing products.

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(12) Single X-ray crystal structures of **1**, **8**, **10J**, **10K**, **12**, **13**, and the des-methyl compound can be found in the Supporting Information
(13) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425.
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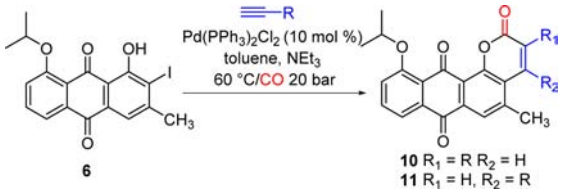
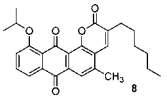
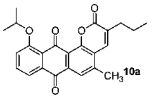
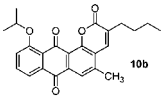
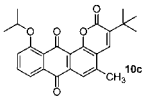
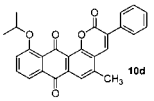
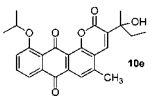
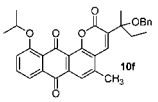
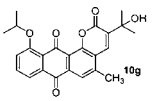
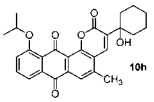
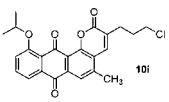
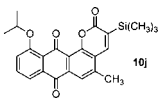
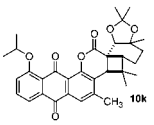
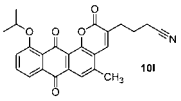
Table 2. Methodological Evaluation of Various Alkynes Domino Alkyne Insertion/Carbonylation/Nu-Acylation Reaction



entry	alkyne	yield	major product	ratio 10	ratio 11
1		82		2.7	1
2		71		3	1
3		76		2	1
4		28		1	0
5		20		>10	1
6		82[a]		1	0
7		85		1[b]	0
8		88		1	0
9		63		1	0
10		94		2	1
11		78		>10	1
12		30[c]		1	0
13		28		1	0

[a] Reaction run under a balloon of CO. [b] In this example, a significant amount of Sonogoshira product was observed. [c] An additional [2 + 2] reaction was observed to afford **10k**; see the Supporting Information.

Previous reports of reactivity in carbonylative reactions involving *ortho,ortho*-disubstituted aryl halides prompted the choice of the PEPPSI-iPr ligand (entry 10);[10,19] however, none of the pyran-4-one ring system was observed.[20] Interestingly, the main byproduct of this reaction, especially when using palladium(0) catalysts, was the dehalogenated compound (see the Supporting Information). Once the optimum conditions for the domino process were established we investigated a series of alkynes to provide insight into the tolerance and scope of this reaction (Table 2). Alkynes containing alkyl groups perform well in the domino process with consistently high yields (entries 1−3). However, the reaction of phenylacetylene was less productive (20%). A range of protected and unprotected alcohols also performed very well in this transformation. High yields resulted in the synthesis of the alkyl chloride **10i** and the vinyl silane **10j**, allowing for two excellent functionalities for further synthetic transformations. Interestingly, the complex alkyne, bearing an olefin, underwent an additional [2 + 2] visible light promoted cycloaddition following workup to produce the heptacycle **10k**. Nitriles and some protected amines were not as high yielding under the general conditions proposed previously and may require additional optimization.

In order to investigate the reasons why no pyran-4-one ring system was formed, we examined a stepwise reaction process. Here we attempted the isolation of the Pd(II) putative catalytic precursor and its subsequent reaction with CO (Scheme 3), reasoning that the early CO insertion was a key step. Treatment of anthraquinone iodide **6** with 1 equiv of $Pd(PPh_3)_4$ in benzene provided isolable crystals of the iodinated oxidative addition product **12** (Figure 1). Treating this iodide (**12**) or the chloride (**13**) under carbonlyative conditions (CO, 20 bar) resulted in recovery of only the organometallic starting materials with no evidence of acyl complex formation.[16] The electronegativity of the halide appears to play no role in the reactivity of the proposed oxidative addition species to carbonylation or the occurrence of a reversible CO insertion exits. The *des*-methyl variant of **12** was also prepared to examine the hypothesis that carbonylation was affected by the sterics of the *ortho,ortho*-disubstitution;[10] however, carbonylation was again ineffective, suggesting that the electronics of the anthraquinone system play a large role in this proposed domino process. We provide a more expansive discussion of the possible mechanism in the Supporting Information.

As an alternative pathway to the synthesis of the pyran-4-one ring system of **1** we were attracted to a new method for pyran-4-one formation through β-keto-sulfoxides as annulation precursors (Scheme 4).[21]

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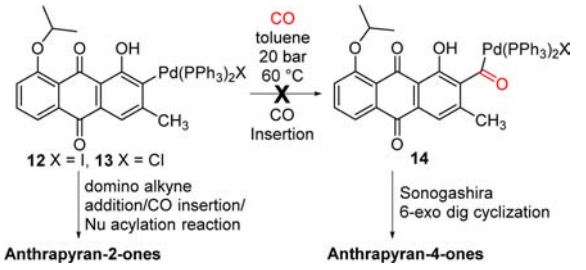
Scheme 3. Attempted CO Insertion of Pd Complexes **12** and **13**



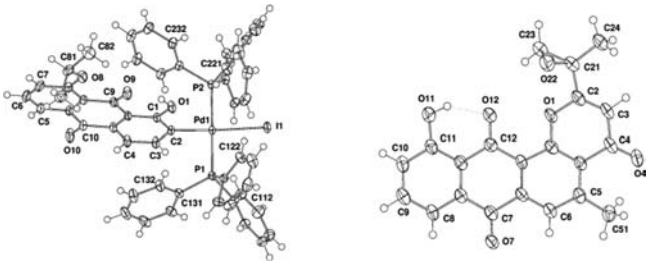
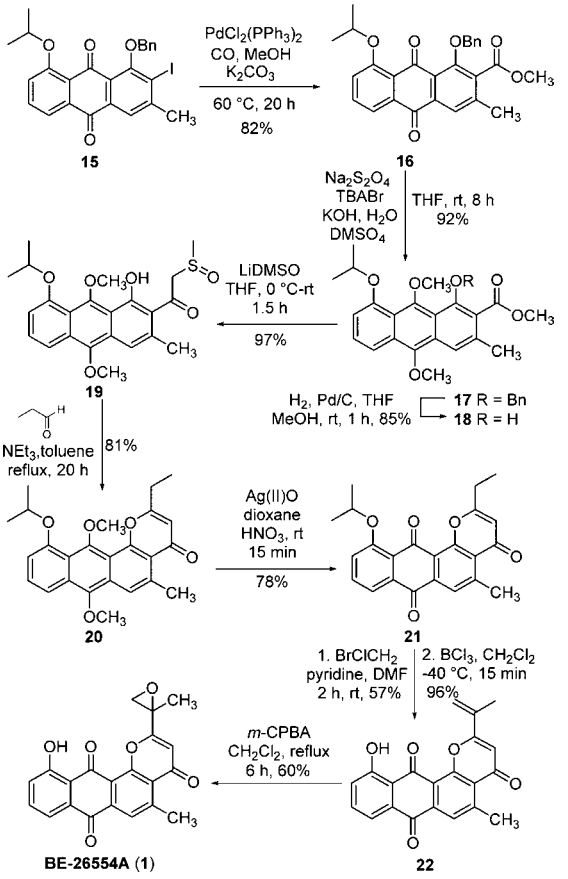


Figure 1. X-ray structures of **12** and (±)-BE-26554A (**1**).

Treatment of the phenol **6** with carbon monoxide, base, and methanol resulted in the formation of the methyl ester in variable yields. Given that alkoxycarbonylation of phenols has been reported,[22] we accordingly benzyl protected this functionality. Alkoxycarbonylation of derivative **15** resulted in efficient conversion to the ester **16** in reproducible yields (ca. 82%). Both protection of the B-ring within compound **16** to the dimethoxyanthracene derivative **17** and subsequent benzyl deprotection proceeded in high yields. The resulting hydrogenolysis product, ester **18**, was treated with lithium methylsulfinylmethide to furnish the β-ketosulfoxide **19** in an excellent yield.[21c] Formation of the pyran-4-one ring system was achieved through reaction of **19** with propionaldehyde and catalytic amounts of piperidine. Oxidative demethylation established the anthraquinone core revealing compound **21**. Following the Augustine olefination procedure,[23] treating the pyranone **21** with a bis(pyridinium) cation species generated from $BrClCH_2$ and pyridine in DMF gave the desired alkene (isolated crude) in 57% yield.[7c] Smooth cleavage of the isopropyl group from the A-ring, revealing phenol **22**, was achieved by treatment with BCl_3. Final epoxidation with *m*-CPBA allowed for the synthesis

Scheme 4. Synthesis of (±)-BE-26554A (**1**)



of the natural product (**1**). The ^1H and ^{13}C spectral data for compound **3** matched those in the early report published by the Banyu Pharma group.

In summary, we have demonstrated a straightforward approach to a new series of anthrapyran-2-ones. Furthermore, the first total synthesis of the bioactive natural product (±)-BE-26554A (**1**) was developed utilizing an efficient β-keto-sulfoxide−annulation procedure for the construction of the pyran-4-one moiety. We intend to use this methodology for the synthesis of the other series of BE-compounds reported and carry out further investigations into their biological activity.

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Supporting Information Available. Experimental data, ^1H and ^{13}C NMR spectra for all the new compounds, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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