New Palladium-Catalysed Access to 3-(1'-Indanylidene) Phthalide, Precursor of the Core of Fredericamycin A

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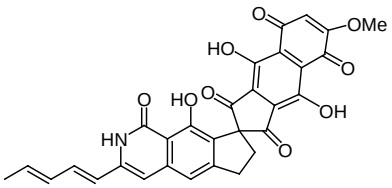
Abstract: An efficient synthesis of 3-(1'-indanilydene) phthalide is described via a palladium-catalysed biscyclisation step.

Key words: palladium, cyclisation, tandem reaction, heterocycle, lactone

Fredericamycin A, isolated from *Streptomyces griseus* in 1981,[1] possesses important biological activities against a large variety of tumours, such as P 388 leukemia, B 16 melanoma, and CD 8F mammary. Furthermore, the Fredericamycin A does not show mutagenicity in the Ames test (Figure).[2]



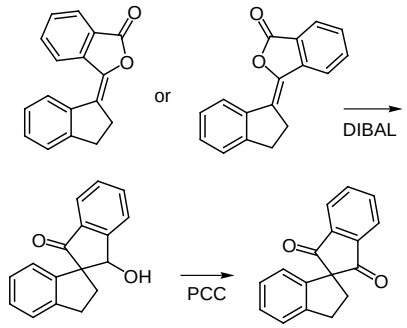
Fredericamycin A

Figure

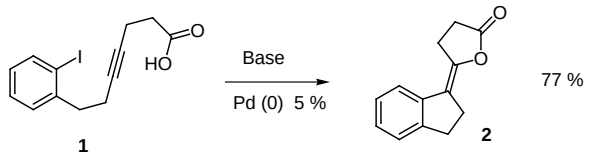
The biological activity mentioned above as well as the unique structure of this hexacycle has prompted several approaches to the construction of this challenging skeleton.[3] However, despite the numerous efforts towards this goal, biological studies have been limited by the rarity of the product.

The crucial step seems to be introduction of the spirocyclic system. One of the ways by which the spirocycle is generated, is the transformation of ylidene phthalides[4a,b] into spirocyclic diketones by a DIBAL reduction of an enol lactone followed by an in situ aldol condensation (Scheme 1).[4c]

As part of our ongoing interest in the construction of polycyclic systems, we have recently reported a new route to γ-arylidenelactones via a tandem carbopalladation-heterocyclisation sequence.[5] In particular, cyclisation of the linear pentynoic acid **1** has led to the indanylidene lactone **2** (Scheme 2).

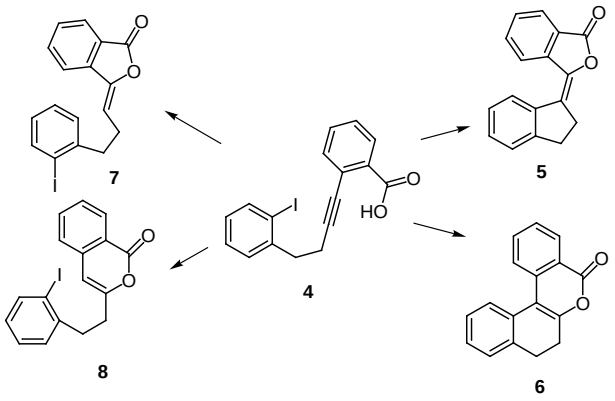


Scheme 1



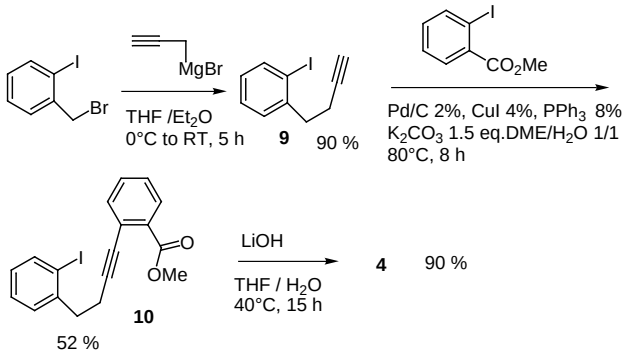
Scheme 2

To further extend the scope of this study, we now wish to describe a novel synthesis for the preparation of 3-(1'-indanylidene) phthalide **5** from linear acid **4**. Moreover, the newly discovered method potentially provides an alternative route to the dibenzo-1,4-diketospiro[4,4]nonane system as shown in Scheme 1. Nevertheless, it was anticipated that application of the same concept to this new system could lead to the formation of four types of products (Scheme 3). Indeed, due to the strain generated by the introduction of an aryl group on the linear system, the palladium-catalysed biscyclisation reaction could either proceed via a five-*exo* or a six-*endo* mode leading to the expected lactone **5** or the isocoumarin **6**, respectively.[14] Two types of direct regioisomeric cyclisation leading to **7** and **8** could also be envisaged, since it is well known that 2-alkynyl benzoic acids are easily transformed into a mixture of phthalides and isocoumarins in the presence of transition metal catalyst including palladium(II) species.[6] With this in mind, when Pd(II) precatalysts are used as source of Pd(0), it becomes important to add a preformed Pd(0)Ln catalyst solution to the reaction mixture.[7]



Scheme 3

The required acid **4** was prepared in three steps from commercially available 2-iodobenzyl bromide (Scheme 4). The major difficulty encountered in the preparation of **4** was the Sonogashira coupling reaction of the known alkyne moiety[8] **9** with methyl *o*-iodobenzoate. Using literature reported methods,[9] very low yields of the expected product resulted (20-30%) along with a complex mixture of uncharacterised byproducts. Nevertheless, a noticeable improvement was made by modifying the coupling procedure,[10] (Pd/C, PPh_3, CuI, DME/H_2O, Δ) where **10** was isolated in 52% yield. Finally, smooth alkaline hydrolysis of the ester with lithium hydroxide in aqueous THF provided **4** in high yield.



Scheme 4

In the first attempt, we used a reaction protocol based on reported methods.[5] Thus, when **4** was treated with a catalytic amount of Pd(0) complex (5% $Pd(OAc)_2$, 10% TFP, 10% heptene) in DMSO at room temperature in the presence of tBuOK as base, only compound **8** resulting from the direct cyclisation of the acid on the triple bond via the 6-*endo* mode was isolated in low yield (14%). A control reaction indicated that in absence of palladium species, after 20 hours at room temperature, traces of product **8** were obtained.

In order to find the optimum conditions for biscyclisation, the effect of the palladium source was first evaluated, (entries 1-5) while other reaction parameters were maintained. The results are shown in Table 1.

Table 1 Influence of the nature of the catalyst

Entry	Source of Pd(0)	Solvent	Product(s)	Yield (%)[b]
1	$Pd(OAc)_2$, TFP[a] heptene	DMSO	**8**	14
2	$Pd(PPh_3)_4$	DMSO	**5** + **6** +**8**	not determined
3	$Pd_2dba_3{\cdot}CHCl_3$ TFP	DMSO	**8**	34
4	$Pd(OAc)_2$, TFP[a] $NaBH_4$	DMSO	**5**	23
5	$PdCl_2(PPh_3)_2$ BuLi	DMSO	-	no reaction
6	$Pd(OAc)_2$, TFP[a] $NaBH_4$	CH_3CN	**8**	38

a) TFP = tris(2-furyl) phosphine; b) All reactions were run at room temperature with *t*BuOK as base.

Of the palladium sources examined, only $Pd(OAc)_2$ reduced by $NaBH_4$[11] in the presence of 2 equivalents of tris(2-furyl) phosphine, afforded the desired product **5** (entry 4). However, although the starting material was consumed, a low yield of tetracyclic phthalide was isolated (23%). Zerovalent palladium formed from $PdCl_2(PPh_3)_2$ by the reduction with BuLi[12] failed to promote the reaction (entry 5). Commercially available catalysts such as $Pd(PPh_3)_4$ (entry 2) and $Pd_2dba_3{\cdot}CHCl_3$ with TFP as ligand (entry 3) were ineffective. The first one led to a mixture of three inseparable compounds **5**, **6** and **8** in the ratio 1/0.1/0.3. The second catalyst used afforded exclusively compound **8** arising from direct 6-*endo* cyclization. All products were easily identified by ^1H NMR, where product **8** gave a singlet at 6.25 ppm for the ethylenic proton and a doublet centered at 8.27 ppm for one aromatic proton. Product **5**, which is a known compound[4b] gives a doublet at 8.32 ppm and product **6** a doublet at 8.39 ppm. The solvent effects were also examined: in the optimized conditions described below, changing the solvent to acetonitrile led to the phthalide **5** as the sole isolable product but the yield was still low (38%). Presumably, the use of a strong base such as *t*BuOK caused degradation of the starting material.

Consequently, we have also studied the biscyclisation reaction of compound **4** with different bases. Results are summarised in Table 2.

We have found that inorganic bases such as potassium or cesium carbonate worked well in DMSO giving 64% of the expected product along with 10% of **6** which was easily removed by recrystallisation.[13] Surprisingly, the use of $KHCO_3$, led to a mixture of products **5** and **6** in excellent yield, where the regioselectivity of the biscyclisation is reversed in favour of **6** (entry 7). It should be noted that the

Table 2 Influence of the nature of the base

Entry	Base	Ligand	Solvent	Product	Yield (%)[a]
1	K_2CO_3	TFP	CH_3CN	mixture of **5/6/8**	not determined
2	K_2CO_3	TFP	DMSO	**5**	55
3	K_2CO_3	PPh_3	DMSO	**5**	61
4	**Cs_2CO_3**	**PPh_3**	**DMSO**	**5**	**64**
5	KF	TFP	DMSO	mixture of **5/6/8**	not determined
6	KOAc	TFP	DMSO	**5**	46
7	$KHCO_3$	PPh_3	DMSO	mixture of **5/6**	86 (33/66)

a) except for entry 5, where the product has been purified by recrystallisation, all yields were determined by ^{1}H NMR. In all cases, minor product **6** is also present in small quantities (5-10%).

use of PPh_3 as ligand in place of TFP significantly improved the reaction efficiency (entry 3).

In conclusion, the palladium-catalysed bis-cyclisation reaction presented herein constitutes a novel and rapid synthetic route to the phthalide nucleus. We are currently investigating an extension of this work to study the role of substituents on aromatic rings, which will be reported in due course.

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(7) Where necessary the Pd(0) catalyst was preformed by reaction of palladium acetate with 2 equivalents of monodentate ligand per Pd in the solvent followed by addition of a reducing agent (1-heptene or $NaBH_4$).

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(13) Typical experimental procedure : Carboxylic acid **4** (100 mg, 0.266 mmol) in 3 mL of DMSO was treated with cesium carbonate (104 mg, 0.319 mmol), the resulting solution was stirred during 15 min. At this time, Pd (0) solution was added (5% $Pd(OAc)_2$, 10% PPh_3, $NaBH_4$ in 2 mL of DMSO). The mixture was further stirred at 25 °C and followed by GC until completion. The mixture is diluted with diethyl ether and washed with brine. The organic layer was dried on Na_2SO_4, condensed in vacuo and the residue chromatographed on silica gel.

(14) Analytical data : ^{1}H and ^{13}C NMR spectra of **5** were identical with those reported in the literature.[4b]
Product **5:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05-3.11 (2H, m); 3.21-3.28 (2H, m); 7.28-7.42 (3H, m); 7.50-7.55 (1H, m); 7.71 (1H, ddd, J = 1.1; 7.7; 8.1 Hz); 7.95-8.02 (2H, m); 8.32 (1H, d, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.28; 33.06; 122.19; 124.57; 125.9; 126.13; 126.19; 126.87; 129.43; 129.65; 130.89; 134.59; 137.75; 138.26; 140.5; 150.38; 167.38. The stereochemistry of **5** was determined using Nuclear Overhauser Effect (NOE) experiments: irradiation of C_4 proton (δ 8.32, d, J = 8.1 Hz) of **5** produced NOE enhancement at the signals of C_5 (15.4%) and C_{14} (10.5%).
NMR data for product **6** have been deducted from mixture of **5**/**6** (entry 7, Table 2). Product **6** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.7-2.82 (2H, m); 2.90-3 (2H, m); 7.1-7.8 (6H, m); 8.12 (1H, d, J = 8.4 Hz); 8.4 (1H, d, J = 8.1 Hz)
Product **8** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (2H, t, J = 8.45 Hz); 3.14 (2H, m); 6.23 (1H, s); 6.90 (1H, m), 7.18-7.25 (3H, m); 7.32 (1H, d, J = 7.7 Hz); 7.46 (1H, m); 7.66 (1H, ddd, J = 1.1; 7.7; 7.7); 7.82 (1H, d, J = 8.1 Hz); 8.26 (1H, d, J = 8.1 Hz).

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