A Highly Efficient Synthesis of Rocaglaols by a Novel α-Arylation of Ketones

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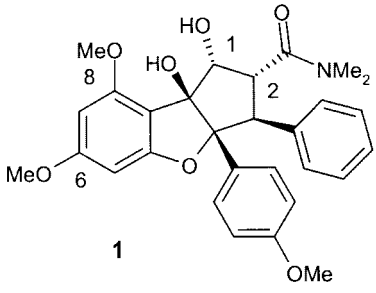
Keywords: α-Arylation of ketones / Drug design / Natural products / Suzuki reaction / Total synthesis

Rocaglaols are natural products exhibiting a range of biological activities. A new synthetic method for the α-arylation of ketones allows for the synthesis of previously inaccessible rocaglaol derivatives. The key sequence consists of a previously unreported Suzuki type reaction using brominated silyl enol ethers as substrates followed by deprotection of the arylated silyl enol ethers.

Introduction

Rocaglamides and rocaglaols are natural products exclusively isolated from the plant genus *Aglaia*, which occurs in the tropical rain forests of Southeast Asia.[1] Since the first isolation of rocaglamide (**1**, Scheme 1) from *Aglaia elliptifolia* and the elucidation of its structure in 1982,[2] more than 50 different rocaglamide congeners, all characterized by a unique cyclopenta[*b*]tetrahydrobenzofuran skeleton, have been identified.[3] Rocaglaol (**2**), which is unsubstituted at C-2, was first isolated in 1993 from the leaves of *Aglaia odorata*.[4] These natural products have recently attracted considerable interest, because they exhibit both insecticidal activity and cytostatic effects against human cancer cells in vitro and furthermore inhibit NF-κB induced gene activation.[1]



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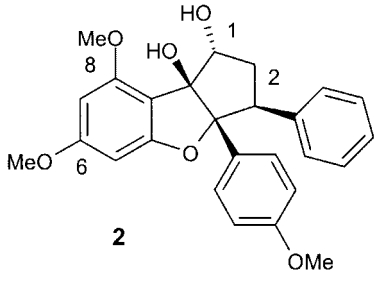

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Scheme 1. Structures of rocaglamide (**1**) and rocaglaol (**2**).

Trost achieved the first total synthesis of enantiomerically pure rocaglamide (**1**) and proved the absolute stereochemistry of the natural product.[5] Several syntheses as well as synthetic studies of rocaglamides and rocaglaols have subsequently been reported, notably by Taylor,[6] Kraus,[7] Watanabe,[8] research groups from Novartis[9] and Bayer,[10] and very recently by Porco,[11] and ourselves.[12] Despite these approaches, the synthesis of rocaglamides and rocaglaols remained a challenging target, since none of them allowed for the derivatization of the benzofuran moiety in a general and efficient way.

Results and Discussion

We now report on the development of a new synthetic method for the α-arylation of ketones, which enabled us to broadly vary the benzofuran moiety of rocaglaols for the first time.

As described by Taylor,[6] the cyclopenta[*b*]tetrahydrobenzofuran skeleton of rocagloals **3** (Scheme 2) can arise very efficiently from an intramolecular pinacol coupling reaction of **4** using samarium diiodide. The aldehyde **4** with the desired *syn*-configuration of the two phenyl moieties can be obtained by the Michael addition of benzofuranones **5** to cinnamaldehyde. However, the synthesis of the key intermediate **5** is limited to very electron-rich benzofuranones which allow Hoesch or Friedel–Crafts type reactions (Scheme 3, path a).[13] Since both methods fail for compounds with less electron donating groups (EDG), no method was known to obtain rocaglaols other than 6,8-dimethoxy- or 6,8-diethoxy-substituted ones. We therefore decided to obtain the key intermediates **5** via α-arylation of benzofuranones **7** (as shown in Scheme 3, path b).

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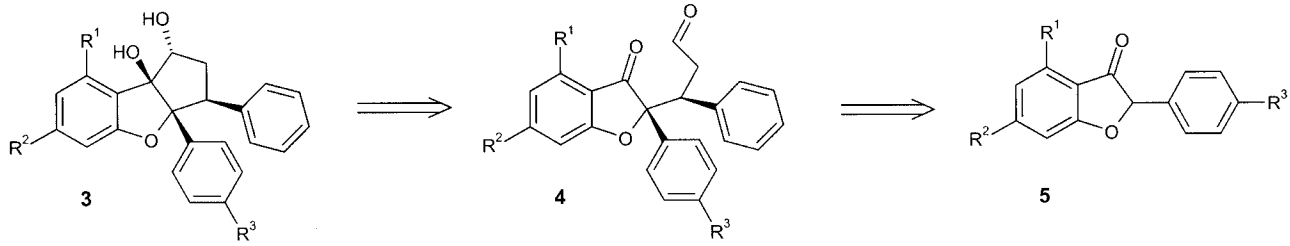
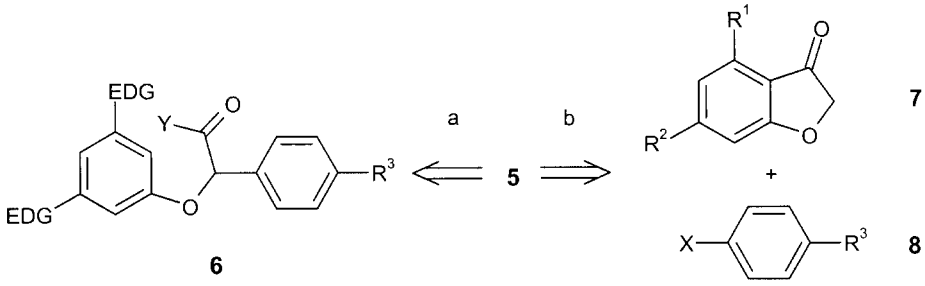


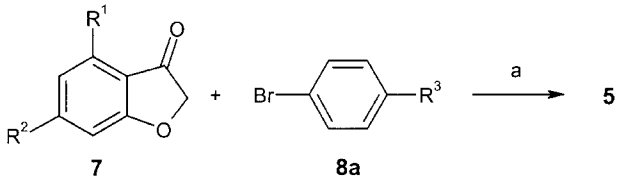
Scheme 2. Retrosynthetic analysis for the synthesis of rocaglaols **3**.



Scheme 3. Retrosynthetic analysis for the key intermediate **5**.

The α-arylation of ketones is still a challenging problem in organic synthesis. The well-known nucleophilic aromatic substitution reaction of a stabilized enolate with an aryl halide requires strong electron-withdrawing substituents on the arene.[14] The more recently discovered nucleophilic radical substitution between an enolate and an aryl halide allows the use of a broader range of substrates.[15] However, solvent limitations, selectivity problems and side reactions are a concern with this method. A number of very effective α-arylating reagents has been developed, but their practical use is diminished by their expensive and time-consuming preparation and by the need to use them stoichiometrically.[16] The most elegant method for the α-arylation of ketones is certainly the recently discovered transition-metal-catalyzed coupling of ketones and aryl halides.[17] Enormous progress has been made in this field by developing several highly efficient ligands,[18] but even this approach has certain drawbacks: a screening for every substrate combination is normally necessary to find the most suitable of many different and often quite expensive ligands. In addition, as our own results show (see below), strong bases such as sodium *tertiary* butoxide are usually needed, which are not always tolerated by the substrates.

In a first approach we chose the α-arylation of benzofuranones **7** via Buchwald coupling (Scheme 4) with aryl bromides **8a** as an alternative route to key intermediate **5**.[19] Several new α-arylated benzofuranones **5** could be obtained using palladium acetate as the catalyst, 2-(dicyclohexylphosphanyl)-2′-methyl-biphenyl as the ligand and sodium *tertiary* butoxide as the base. The method is applicable to more derivatives than the Friedel–Crafts type reactions mentioned before, but is still limited to electron-rich compounds. The moderate yields and the failure to synthesize mono-alkoxy derivatives or unsubstituted benzofuranones are due to lability of both the substrate and the resulting products in the presence of strong bases, which are needed for the coupling reaction. With weaker bases the reaction did not proceed.



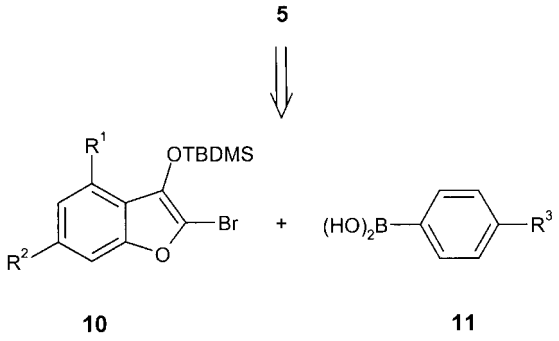
	R^1	R^2	R^3	**5**
a	MeO	MeO	Me	50%
b	MeO	MeO	MeO	35%
c	MeO	MeO	H	21%
d	Me	MeO	Me	39%
e	Me	Me	Me	51%
f	Me	Me	MeO	22%
g	Me	Me	H	15%

Scheme 4. α-Arylation of benzofuranones **7** via Buchwald coupling. a) $Pd(OAc)_2$, **9**, NaO*t*Bu, toluene or THF, 60–80 °C.

We then envisioned that the desired substituted benzofuranones **5** could be synthesized by a Suzuki type reaction of brominated silyl enol ethers **10** with aryl boronic acids **11** followed by deprotection under acidic conditions (Scheme 5).

Our new Suzuki approach proved to be a very efficient and generally applicable route for the formation of the desired α-arylated benzofuranones **5** under mild conditions (Scheme 6).

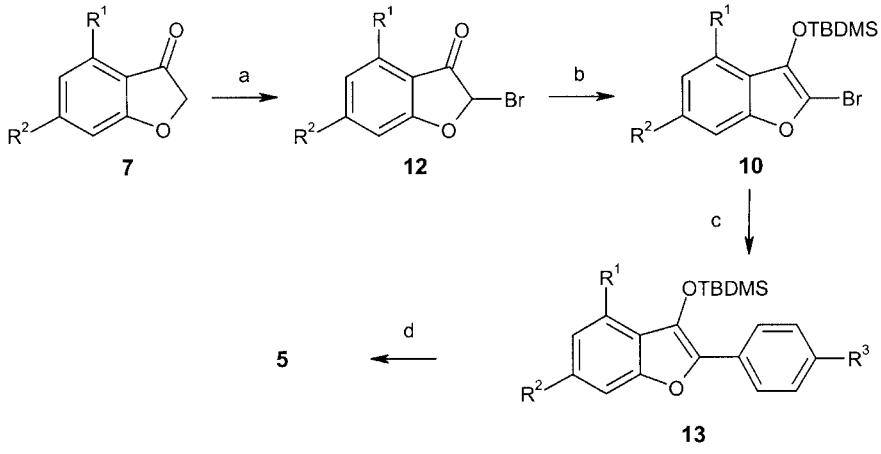
The substituted benzofuranones **7** are easily available by intramolecular Friedel–Crafts acylation or in a very efficient one-pot-procedure by the silylation of 2-hydroxy-



Scheme 5. Retrosynthetic analysis for the synthesis of α-arylated benzofuranones **5** via Suzuki type coupling.

acetophenones, followed by bromination of the resulting silyl enol ether and ring closure of the formed α-bromo-acetophenone.[20] α-Bromination of the benzofuranones **7** could be achieved with $CuBr_2$ in a mixture of ethyl acetate and chloroform[21] or with bromine in a mixture of diethyl ether and dioxane to afford the α-bromobenzofuranones **12** in good yields.[22] The silyl enol ether **10** was then formed using *tert*-butyldimethyl silyl triflate in diethyl ether or toluene. This procedure leads to a two-phase mixture and allows for the separation of the brominated silyl enol ethers from the salts formed by simple separation of the two phases.[23] It is reliably applicable up to multi-gram scale. The silyl enol ethers **10** could be isolated and purified, but it was also possible and more convenient to use the separated toluene solution directly, without further purification in the subsequent Suzuki type reaction.

This Suzuki type reaction proceeds under standard conditions using bis(triphenylphosphane)palladium dichloride or tetrakis(triphenylphosphane)palladium as the catalyst and sodium carbonate as the base in a toluene/water mixture. Typically, reaction times of two to four hours at a temperature of 90 to 95 °C were sufficient for complete conversion. Notably, silyl enol ethers **10** of unsubstituted benzofuranones and of benzofuranones with electron-withdrawing or electron-donating substituents could be converted with high yields. Desilylation of the products of the Suzuki reaction **13** was achieved under acidic conditions with either trifluoroacetic acid or HCl in dioxane. Deprotection with tetrabutyl ammonium fluoride (TBAF) was a less favourable alternative because of the sensitivity towards oxidation of most of the α-aryl-benzofuranones **5** under basic conditions. Using HCl in dioxane, the solvent could simply be evaporated and the crude reaction mixture was used without further purification.



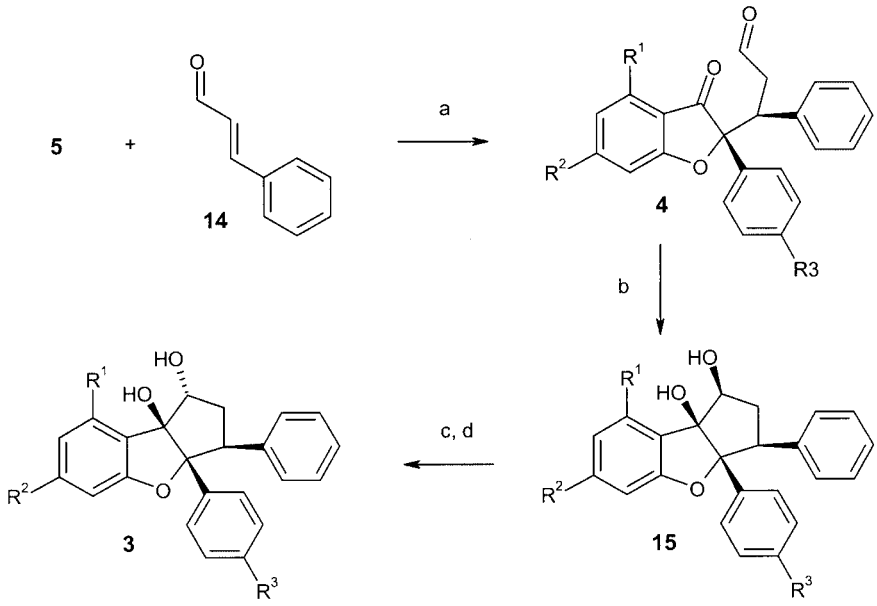
	R^1	R^2	R^3	12	10	13	5
h	H	H	Cl	50% (A)	*	69% (C)	73% (G)
i	H	F	Cl	66% (A)	46%	98% (C)	63% (G)
j	H	Cl	Cl	48% (A)	*	60% (C)	* (G)
k	H	F_3CO	Cl	51% (A)	81%	90% (D)	* (E)
l	H	BnO	Cl	40% (B)	*	77% (D)	* (F)
m	F	F	Cl	74% (A)	82%	84% (D)	* (E)
n	Cl	Cl	Cl	84% (A)	*	68% (D)	* (E)
o	H	BnO_2CHN	Cl	78% (B)	*	90% (D)	* (E)
p	$Cl(CH_2)_2O$	H	Cl	77% (B)	46%	75% (D)	* (F)
q	$MeO(CH_2)_2O$	H	Cl	84% (B)	99%	68% (D)	* (F)
r	H		Cl	32% (A)	*	64% (D)	* (E)

Scheme 6. α-Arylation of benzofuranones **7** via Suzuki coupling. a) **A**: $CuBr_2$, EtOAc, $CHCl_3$; **B**: Br_2, Et_2O, dioxane; b) TBDMSOTf, NEt_3, toluene or Et_2O; c) *para*-chloro phenyl boronic acid, Na_2CO_3, toluene; **C**: $Pd(PPh_3)_2Cl_2$, 90 °C; **D**: $Pd(PPh_3)_4$, 95 °C; d) **E**: TFA; **F**: HCl, dioxane; **G**: TBAF; * converted without purification.

The α-arylated benzofuranones **5** were used as nucleophiles in a Michael addition with cinnamaldehyde (**14**) to give two diastereomeric addition products, which could be separated via chromatography (Scheme 7). The yield of the desired epimer **4** could be increased by isomerization of the undesired epimer under Michael addition conditions. Cyclization by pinacol coupling with samarium diiodide provides selectively the *cis*-diols **15**. Swern oxidation and diastereoselective reduction with tetramethylammonium triacetoxy borohydride gave the analogous ketones and *trans*-diols **3**, respectively. These *trans*-diols **3** can be converted into the corresponding rocaglamides according to literature procedures.[9]

Conclusions

In summary, rocaglaol derivatives **3** were successfully synthesized from easily available benzofuranones **7**. The key sequence was a new synthetic method for the α-arylation of ketones consisting of a Suzuki type reaction of brominated silyl enol ethers **10** with aryl boronic acids followed by deprotection of the arylated silyl enol ethers **13** under acidic conditions. This efficient and generally applicable approach offers a significant improvement over other reported rocaglaol syntheses because it allows for the broad variation of the benzofuran moiety of rocaglaols for the first time.



	R^1	R^2	R^3	**4**	**15**	**3**
a	MeO	MeO	Me	---	11%*	n.d.
b	MeO	MeO	MeO	n.d.	n.d.	n.d.
c	MeO	MeO	H	52%	28%	23%
d	Me	MeO	Me	29%	14%	34%
e	Me	Me	Me	14%	20%	62%
f	Me	Me	MeO	14%	73%	34%
g	Me	Me	H	13%	31%	n.d.
h	H	H	Cl	10%	21%	n.d.
i	H	F	Cl	5%	34%	35%
j	H	Cl	Cl	31%	15%	n.d.
k	H	F_3CO	Cl	12%	53%	n.d.
l	H	BnO	Cl	51%	54%	n.d.
m	F	F	Cl	27%	35%	69%
n	Cl	Cl	Cl	20%	24%	63%
o	H	BnO_2CHN	Cl	44%	94%	66%
p	$Cl(CH_2)_2O$	H	Cl	28%*	55%	44%
q	$MeO(CH_2)_2O$	H	Cl	8%*	---	12%**
r	H		Cl	26%*	35%	79%

Scheme 7. Synthesis of rocaglaols **3** from α-arylated benzofuranones **5**. a) NaOMe, MeOH; b) SmI_2, THF; c) SO_3·pyridine, NEt_3, DMSO; d) $Me_4N(OAc)_3BH$, HOAc, MeCN; n.d.: not done; * yield over two steps; ** **4q** directly gives **3q**.

Acknowledgments

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